

# Enantioselective Catalysis Through 3,3'-reductive Elimination of Unsaturated Allyl Metal Complexes

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Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

ENANTIOSELECTIVE CATALYSIS  
THROUGH 3,3'-REDUCTIVE ELIMINATION  
OF  
UNSATURATED ALLYL METAL COMPLEXES

by

PING ZHANG

submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

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# Abstract

This dissertation aims to design and develop novel and synthetically useful catalytic enantioselective C-C bond-forming reactions that employ a newly uncovered 3,3'-reductive elimination of bis(allyl)metal species. This elementary transformation allows for new routes for the enantioselective construction of a range of important motifs found in natural products. Enantiomerically enriched *Z*-allylic alcohols are readily accessed through the Ni-catalyzed allylation of *trans,trans*-dienals. Importantly, the first example of branch- and enantioselective allyl-allyl cross-coupling is presented as well, suitable for the construction of compounds bearing tertiary and quaternary carbon centers. With the aim to broaden the application of above described transformations, this dissertation also presents the development of highly efficient and convenient methods for the syntheses of substituted and functionalized allylic boronates.

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Though only my name appears on the cover of this dissertation, a great many people have contributed to its production. I owe my gratitude to all those people who have made this dissertation possible and because of whom my graduate experience has been one that I will cherish forever.

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## LIST OF ABBREVIATIONS

Å	angstrom
Ac <sub>2</sub> O	acetic anhydride
AcOH	acetic acid
aq	aqueous
BBN	borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-binaphthalene-2,2'-diol
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Boc <sub>2</sub> O	di- <i>t</i> -butyl dicarbonate
Bn	benzyl
B <sub>2</sub> (pin) <sub>2</sub>	bis(pinacolato)diboron
<i>n</i> -BuLi	<i>n</i> -butyllithium
<i>t</i> -BuLi	<i>t</i> -butyllithium
Bz	benzoyl
Bz <sub>2</sub> O	benzoic anhydride
cod	1,5-cyclooctadiene
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
dba	dibenzylideneacetone
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride

DIOP	4,5-bis(diphenylphosphino-methyl)-2,2-dimethyl-1,3-dioxolane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethyl- <i>N,N'</i> -trimethyleneurea
DMSO	dimethyl sulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
dppb	1,4-bis(diphenylphosphino)butane
dpp-benzene	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
dppm	1,1-bis(diphenylphosphino)methane
d.r.	diastereomeric ratio
D- <i>t</i> -BPF	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
ee	enantiomeric excess
e.r.	enantiomeric ratio
eq.	equation
equiv	equivalents
Et-DuPhos	1,2-bis(2,5-diethylphospholano)benzene
EtOAc	ethyl acetate
EtOH	ethanol
GLC	gas-liquid chromatography

HG-II	Hoveyda-Grubbs catalyst 2 <sup>nd</sup> generation
HPLC	high performance liquid chromatography
LAH	lithium aluminum hydride
Me-DuPhos	1,2-bis(2,5-dimethylphospholano)benzene
MeOH	methanol
MS	molecular sieves
NBO	natural bond orbital
nbđ	norbornadiene
NHC	N-heterocyclic carbene
Ni(acac) <sub>2</sub>	nickel(II) acetylacetonate
Ni(cod) <sub>2</sub>	bis(1,5-cyclooctadiene)nickel
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance spectroscopy
PCy <sub>3</sub>	tricyclohexylphosphine
Pd <sub>2</sub> (dba) <sub>3</sub>	tris(dibenzylideneacetone)dipalladium
pin	pinacol
PPh <sub>3</sub>	triphenylphosphine
<i>i</i> Pr-DuPhos	1,2-bis(2,5-di- <i>i</i> -propylphospholano)benzene
Py	pyridine
RCM	ring-closing metathesis
r.t.	room temperature
SFC	supercritical fluid chromatography

TADDOL	2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	Trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TPAP	tetrapropylammonium perruthenate
TsOH	<i>p</i> -toluenesulfonic acid
QuinoxP*	2,3-bis( <i>tert</i> -butylmethylphosphino)quinoxaline

# Chapter I

## Ni-Catalyzed Enantioselective Allylation of Dienals

### I. INTRODUCTION

Stereoselective addition of allyl groups to ketones and aldehydes is an important method in the construction of open-chain systems bearing sequential stereocenters.<sup>1</sup> This method features plenty of benefits, such as high levels of diastereo- and enantioselectivity, an extreme diversity of reagents, ability to access different stereodyads and triads, and provides latent functionality in the homoallylic alcohol product. Collectively, these features make allylation protocols ideal for synthetic planning.<sup>1a,1d</sup>

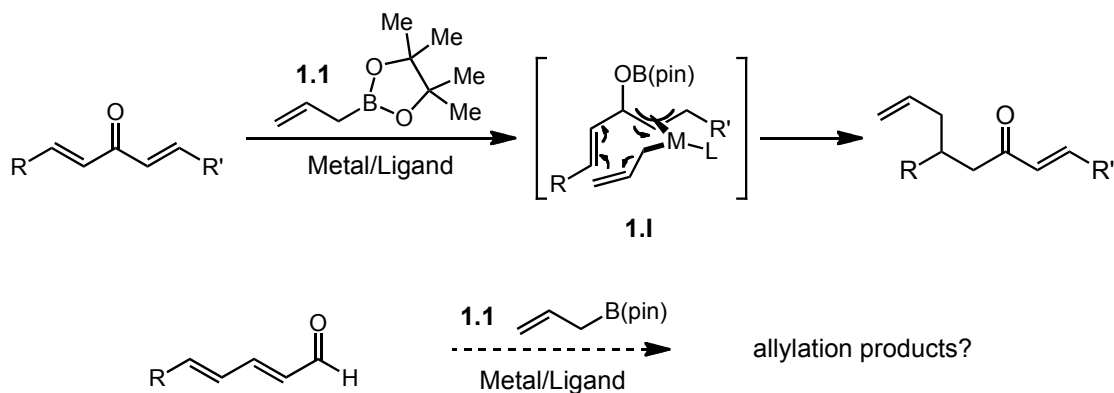
Recent studies in the Morken group have focused on expanding the range of allylation reactions. In this effect we have realized novel reactivities between dialkylidene ketones and allylboronic acid pinacol ester [allylB(pin), **1.1**] in the presence of Ni or Pd. A 3,3'-reductive elimination of bis(allyl)metal complexes (such as **1.I** in Scheme 1.1) is believed to be involved and is responsible for regioselectivity.<sup>2</sup> In light of the structural requirements of transition state **1.I**, we envisioned that dienals might access similar intermediates which allow for 3,3'-reductive elimination and enable new types of allylation reactions. These studies are the focus of this chapter.

---

<sup>1</sup> For recent reviews of catalytic enantioselective carbonyl allylation, see: (a) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (b) Hall, D. G. *Synlett* **2007**, 1644. (c) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2761.

<sup>2</sup> (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

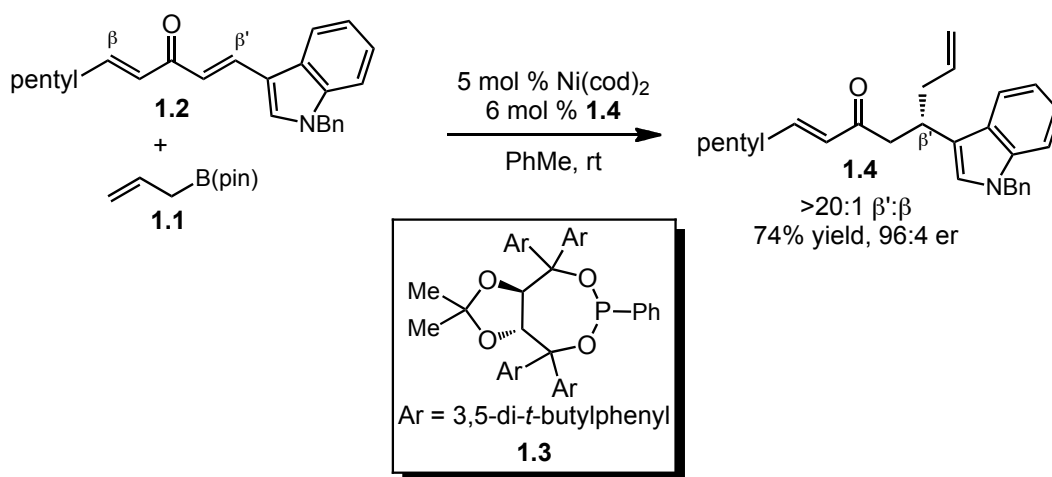
## Scheme 1.1



## II. BACKGROUND

**A. Conjugate Allylation of Activated Enones.** Recently the Morken group has reported the Ni- and Pd-catalyzed enantioselective addition of allylB(pin) (**1.1**) to dialkylidene ketones (e.g. **1.2**).<sup>2a</sup> As depicted in Scheme 1.2, the allyl group selectively adds to the  $\beta'$  carbon and delivers the product in excellent optical purity. Notably, simple enones and their derivatives are inert under the reaction condition.

## Scheme 1.2



While allylic boronates typically undergo 1,2-allylation with carbonyl electrophiles, in the presence of transition metal catalysts, dialkylidene ketones participate in 1,4-conjugate addition reactions. The reaction mechanism postulated to explain this novel reactivity is believed to proceed by Lewis acid induced oxidative addition of Ni(0) [or Pd(0)] to the enones,<sup>3</sup> wherein allylB(pin) (**1.1**) serves as Lewis acid, as depicted in Scheme 1.3. Upon formation of allyl-metal complex **1.II**, transmetallation happens between the activated allylB(pin) and Ni(II) and yields the bis(allyl)Ni(II) species **1.III**. Based on the unique enone activation from the adjacent alkene, it is proposed that the carbon-carbon bond forms by reductive elimination between the  $\beta$  carbon of second alkene and the  $\gamma$  carbon of the  $\eta^1$ -allyl ligand. This hypothesis is supported by the computational studies done by Echavarren, which suggests that the reductive elimination of bis( $\eta^1$ -allyl)(PH<sub>3</sub>)<sub>2</sub>Pd complexes at the two distal carbons (C3 and C3'). This is significantly more facile than 1,1' reductive elimination.<sup>4</sup> In addition, DFT calculations by our group suggest that a simplified model of **1.III** faces a small barrier for a reductive coupling as shown (Scheme 1.3).<sup>2a</sup>

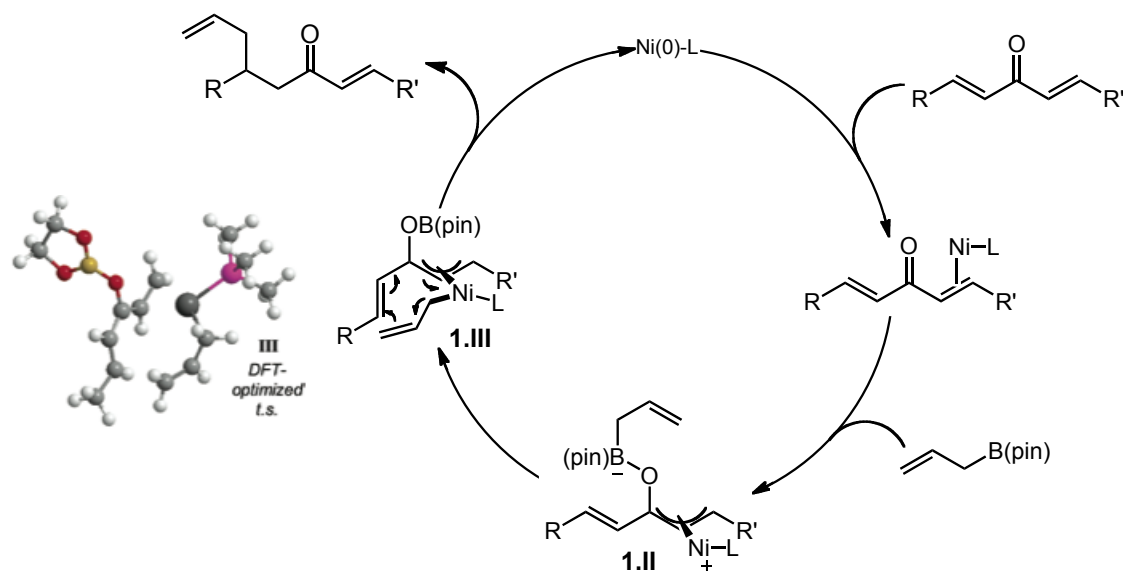
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<sup>3</sup> Supported by related observations: (a) Morita, M.; Inoue, K.; Ogoshi, S.; Kurosawa, H. *Organometallics* **2003**, 22, 5468. (b) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, 123, 1944. (c) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, 113, 6172. (d) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, 114, 5160.

<sup>4</sup> Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, 8, 3620.

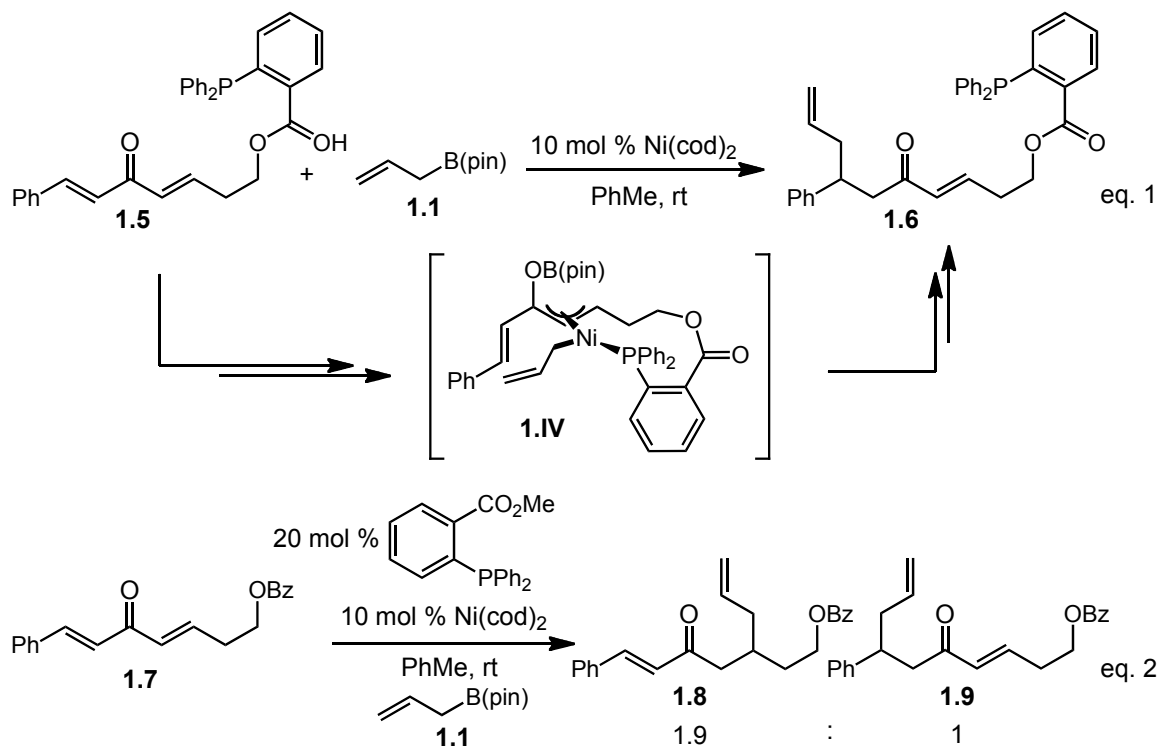


**Scheme 1.3**



The relevance of this elementary step has been further supported by experimental studies.<sup>1b</sup> As illustrated in Scheme 1.4, dialkylidene ketone **1.5**, possessing an internal phosphine ligand, was converted to the allylation adduct wherein allyl addition occurs distal to the phosphine and gives a single product (equation 1). In this reaction, no external ligand was employed, suggesting that the  $\eta^3$ -allyl ligand forms on the alkene proximal to the phosphine and this results in allyl addition to the other alkene (likely through **1.IV**). As a control, ketone **1.7** completely lacks regiocontrol, delivering conjugate allylation products as a 1.9:1 mixture of regioisomers, presumably due to the absence of the intramolecular phosphine ligation in **1.IV**. (Scheme 1.4)

**Scheme 1.4**



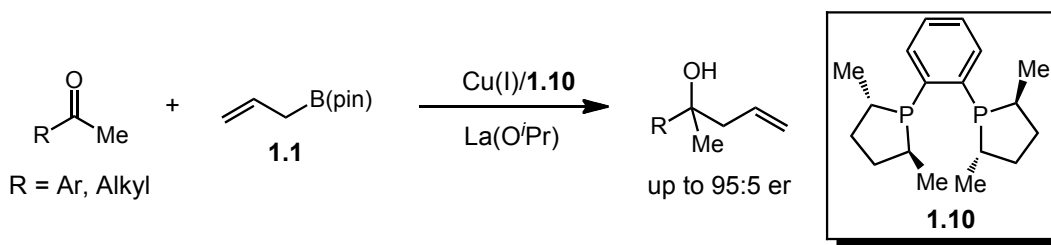
**B. Representative Examples of Metal Catalyzed Enantioselective Allylation of Ketones Through the Use of Allylboron Reagents.** Allylic boronates are versatile building blocks that are relatively non-toxic, readily available and air-stable. These reagents usually add to carbonyl compounds through a chair-like transition state, thereby affording homoallylic alcohols in high levels of diastereoselectivity. Although the Brown methodology,<sup>5</sup> as well as many other methods that utilizing chiral boranes and boronic

<sup>5</sup> For representative examples: (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (c) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

esters,<sup>6</sup> have proven reliable for more than two decades in the synthesis of optically pure complex molecules, they require stoichiometric amount of a chiral director. Therefore enantioselective allylations that require only a catalytic amount of chiral catalyst have been developed. These reactions often rely on chiral Lewis acids<sup>7</sup> or Brønsted acids<sup>8</sup> for prochiral face discrimination and rate acceleration. More recently, metal-mediated allylation of carbonyl compounds has also been explored and proved valuable.<sup>9-11</sup>

The first catalytic enantioselective allylboration of ketones mediated by metal catalysts was developed by Kanai, Shibasaki and co-workers. In this reaction, the complex of Cu(I) with *i*-Pr-DuPHOS (**1.10**) served as a chiral catalyst and La(O*i*-Pr)<sub>3</sub> as a co-catalyst.<sup>9</sup> A panel of ketones underwent allylation smoothly and selectively under these conditions. An allylcopper intermediate was proposed to be the active nucleophile, with the fundamental role of La(O*i*-Pr)<sub>3</sub> being to facilitate dynamic ligand exchange. CrotylB(pin) was also examined in this reaction, for which, diastereoselectivity was significantly affected by the ligand employed.

**Scheme 1.5**



<sup>6</sup> For representative examples: Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.

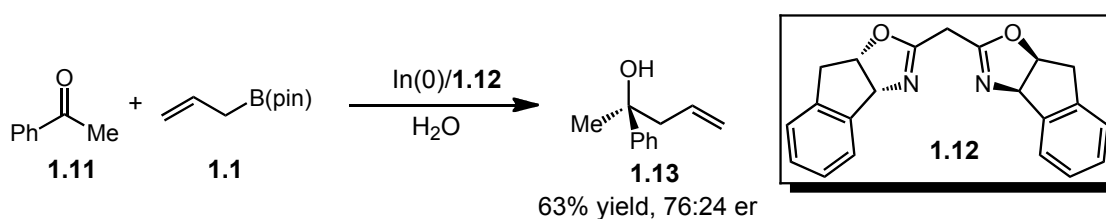
<sup>7</sup> For representative examples: Ishiyama, T.; Ahiko, T.; Miyaaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.

<sup>8</sup> For representative examples: (a) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12650. (b) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.

<sup>9</sup> (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (b) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055. (c) Shi, S.; Xu, L.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638.

In another example, In(0) catalyzed enantioselective allylation of acetophenone with allylB(pin) (**1.1**) was reported.<sup>10</sup> Employing In(0) and chiral bis(oxazoline) ligand **1.12** as catalyst in water, tertiary allylic alcohol **1.13** was yielded. Transmetalation at the indium metal surface was assumed to account for the reactivity. Although the enantiopurity of **1.12** is lower than synthetically useful levels, this example still represents the best catalytic enantioselective allylation of acetophenone in water.

#### Scheme 1.6

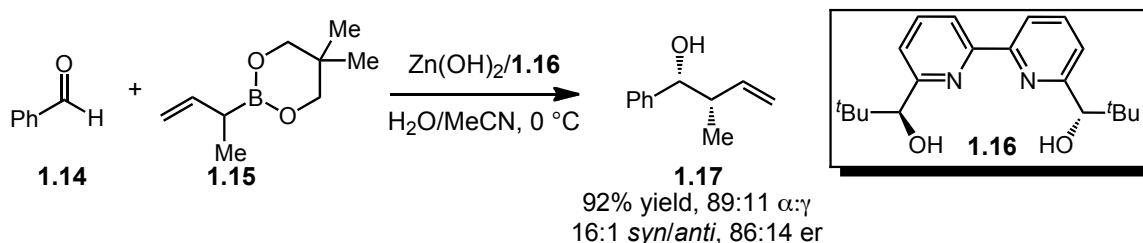


Note that both examples mentioned above employ ketones as substrates, presumably because of the instantaneous reaction between aldehydes and allylic boronates without catalysis. This high reactivity was recently surpassed by a zinc-catalyzed crotylation developed by Kobayashi and co-workers. As a consequence of the smooth crotylation mediated by Zn(OH)<sub>2</sub>, a chiral bipyridine ligand (**1.14**) was utilized as the chiral director and ultimately delivered various homoallylic alcohols with high levels of enantioselectivity (Scheme 1.7). Although the reaction mechanism has not yet been elucidated, a double  $\gamma$ -addition process is believed to operate, which explains the observed regioselectivity very well. Another characteristic feature of this reaction is that

<sup>10</sup> Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, 130, 13824.

the reactions proceed smoothly in aqueous media, where water is believed to facilitate release and regeneration of the catalyst from the products.

**Scheme 1.7**



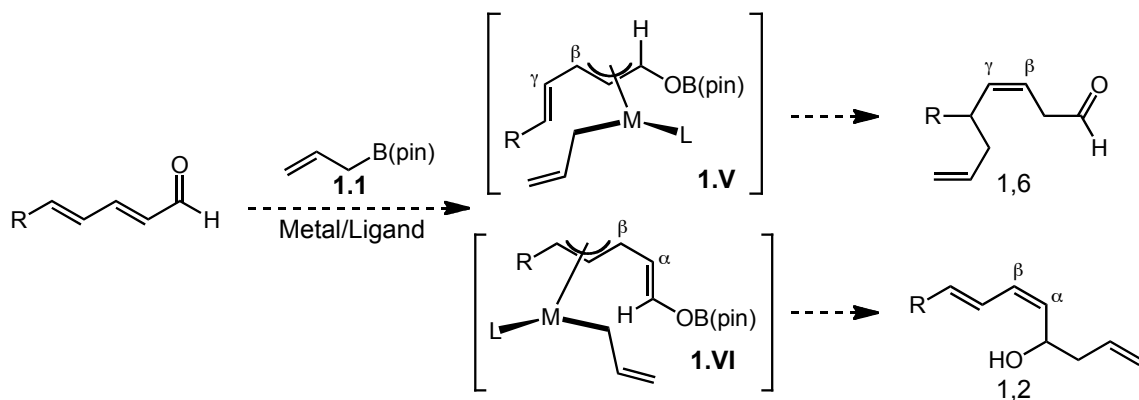
### III. THE DEVELOPMENT OF NI-CATALYZED ENANTIOSELECTIVE ALLYLATION OF DIENALS

**A. Identification of the Optimal Conditions.** Inspired by Ni(0)- and Pd(0)-catalyzed conjugate allylation of dialkylidene ketones, a reaction that is enabled by the low barrier 3,3'-reductive elimination of bis(allyl)metal species, we envisioned that dienals, that meet the structural requirements for high reactivity, might access similar intermediates which allow for 3,3'-reductive elimination. This would furnish transformations that are not readily accomplished by other catalytic allylations.

Based on the key intermediate proposed for conjugate allylation (**1.III**), complexes **1.V** and **1.VI** were expected to be formed from  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (Scheme 1.8). Upon reductive elimination, 1,2-allylation products will be formed from **1.VI**, whereas **1.V** will deliver 1,6-conjugate addition adducts. To be consistent with the mechanistic hypothesis for the conjugate allylation, wherein the DFT calculations suggest a *s-cis* configuration of the alkene in **1.III** (Scheme 1.3), analogous

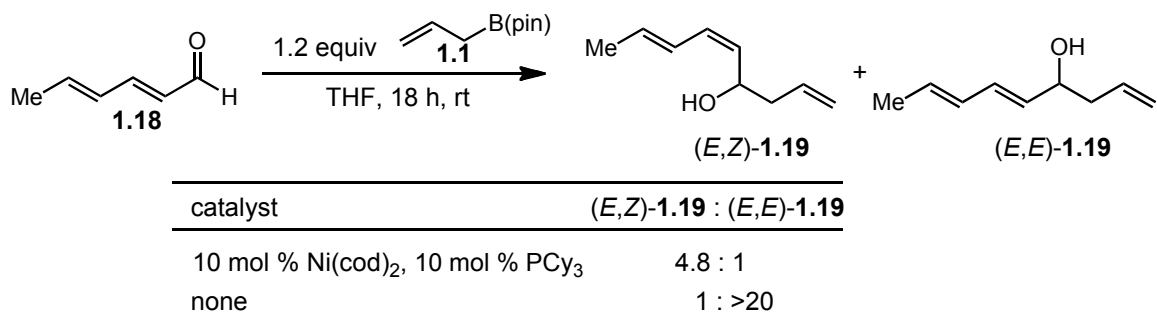
carbon-carbon bond rotations ( $C\beta-C\gamma$  in **1.V** and  $C\alpha-C\beta$  in **1.VI**) might also occur, such that alkene isomerization is expected in allylation products.

**Scheme 1.8**



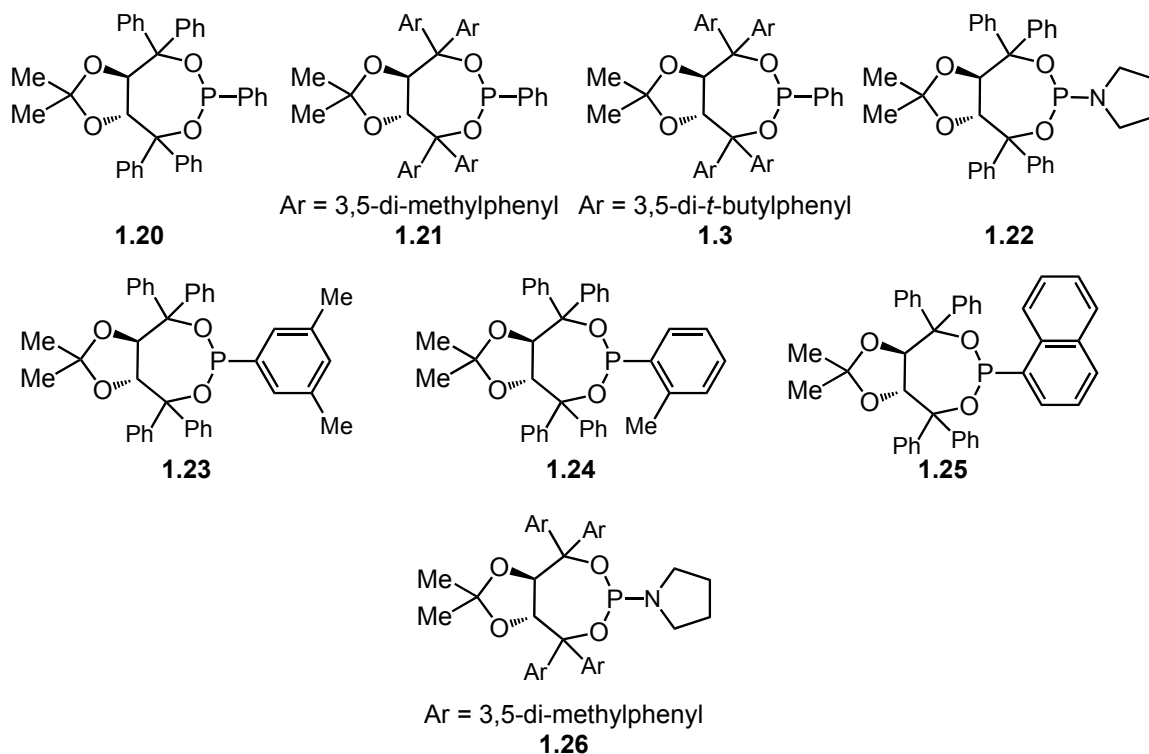
To investigate the rapidity with which catalysis of the dienal allylation might proceed, the reaction between commercially available sorbic aldehyde (**1.18**) and allylB(pin) (**1.1**) was examined (Scheme 1.9). These reactants undergo non-catalyzed reaction at room temperature in THF solvent, achieving greater than 95% conversion to (*E,E*)-**1.19** after 15 hours. Remarkably, in the presence of  $Ni(cod)_2$  and  $PCy_3$ , the reaction is complete in 40 min, and (*E,Z*)-**1.19** rather than the 1,2 addition product (*E,E*)-**1.19** is the predominant reaction product.

**Scheme 1.9**



The efficient catalytic pathway allows us to realize enantioselective transformation by employing chiral ligands. Since TADDOL-derived phosphine ligands have shown utility in the Ni-catalyzed conjugated allylation,<sup>2b</sup> a panel of phosphonites and phosphoramidites were synthesized (Figure 1.1). These ligands present variations on the TADDOL backbone and the substitution of phosphorus, the structural features that most often affect reaction outcome.

**Figure 1.1 TADDOL-Derived Ligands**

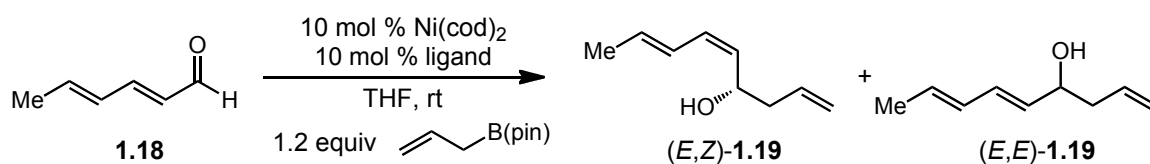


The evaluation of TADDOL-derived phosphine ligands in the Ni-catalyzed allylation of dienals is given in Table 1.1. Remarkably, the catalyzed 1,2-allylation is substantially more efficient when the chiral ligands **1.20-1.26** and **1.3** are employed, affording *E,Z*-isomers exclusively (except entry 1). With regard to enantiocontrol, although all the ligands listed above are effective chiral promoters, phosphonites are superior to phosphoramidites (entry 1 *vs* entry 4, entry 2 *vs* entry 8) and a simpler TADDOL backbone is better than bulkier ones (entry 1 *vs* entries 2 and 3). Thus phosphonite **1.20** is found to be optimal: in THF at room temperature, a 65% yield of alcohol (*E,Z*)-**1.19** was obtained with an enantiomeric purity of 86:14 *er*. Notably, the



reaction with ligand **1.20** occurs rapidly at room temperature, with complete conversion in 25 minutes. The high rate of this reaction suggested that it might proceed efficiently even at lower temperature. Indeed, at -35 °C, the catalytic reaction still occurred, and while 18 h was required to achieve complete conversion, the enantioselectivity and olefin stereoselectivity were enhanced significantly (entry 9). Further modification of the aromatic substituent on phosphorus did not prove advantageous (entries 5-7). Therefore **1.20** was chosen for a study of the reaction scope.

**Table 1.1 Ligand Survey and Optimization of Reaction Condition**



entry	ligand	%yield	(E,Z):(E,E)	er
1	<b>1.20</b>	65	13:1	86:14
2	<b>1.21</b>	65	>20:1	74:26
3	<b>1.3</b>	62	20:1	60:40
4	<b>1.22</b>	60	>20:1	76:24
5 <sup>a</sup>	<b>1.23</b>	79	>20:1	94:6
6 <sup>a</sup>	<b>1.24</b>	75	>20:1	95:5
7 <sup>a</sup>	<b>1.25</b>	87	>20:1	89:11
8	<b>1.26</b>	59	>20:1	63:37
9 <sup>a</sup>	<b>1.16</b>	84	>20:1	94:6

<sup>a</sup> Reaction was cooled to -35 °C.

## B. Substrate Scope of the Ni-Catalyzed Enantioselective Allylation of Dienals.

With the optimized condition, a series of  $\delta$ -substituted dienals were synthesized and

studied. As shown in Table 1.2, dienals bearing a variety of substitutions on the  $\delta$ -carbon participate in the Ni-catalyzed enantioselective allylboration reaction. For all the substrates examined, only 1,2-products were observed, with predominate *E,Z* olefin isomers (except for **1.32**), which is consistent with our mechanistic proposal (Scheme 1.8). Impressively, the stereoselectivity is dependent upon the diene substituents even when these groups are five atoms away from the newly formed stereocenter. Both alkyl and aromatic substituents are well tolerated in the reaction, affording *E,Z*-allylic alcohols in excellent enantioselectivity. The dienals bearing protected alcohol functionalities, however, are not as selective, wherein significant amount of *E,E*-olefin isomers are formed (entries 5 and 6).

**Table 1.2 Substrate Scope**

10 mol % Ni(cod)<sub>2</sub>  
10 mol % **1.20**  
THF, 18 h, -35 °C

**1.1**  
1.2 equiv

entry	substrate	product	%yield <sup>a</sup>	( <i>E,Z</i> ):( <i>E,E</i> )	er
1	 <b>1.27</b>	 <b>1.33</b>	76	>20:1	95:5
2	 <b>1.28</b>	 <b>1.34</b>	92	>20:1	97:3
3	 <b>1.29</b>	 <b>1.35</b>	66	>20:1	96:4
4	 <b>1.30</b>	 <b>1.36</b>	81	10:1	97:3
5	 <b>1.31</b>	 <b>1.37</b>	93	4:1	78:12
6	 <b>1.32</b>	 <b>1.38</b>	80	1:2	97:3

<sup>a</sup> Yield refers to the mixture of two isomers if applicable.

Due to the importance of oxygenated functionalities in organic synthesis, efforts were taken to further modify the reaction condition and allow for more selective reactions with substrates such as **1.31** and **1.32**. It was noticed that the *E,E* olefin isomers, when observed, are always racemic, suggesting that they arise from the non-catalyzed allylboration of aldehydes. It was considered that conditions that accelerate the rate of the

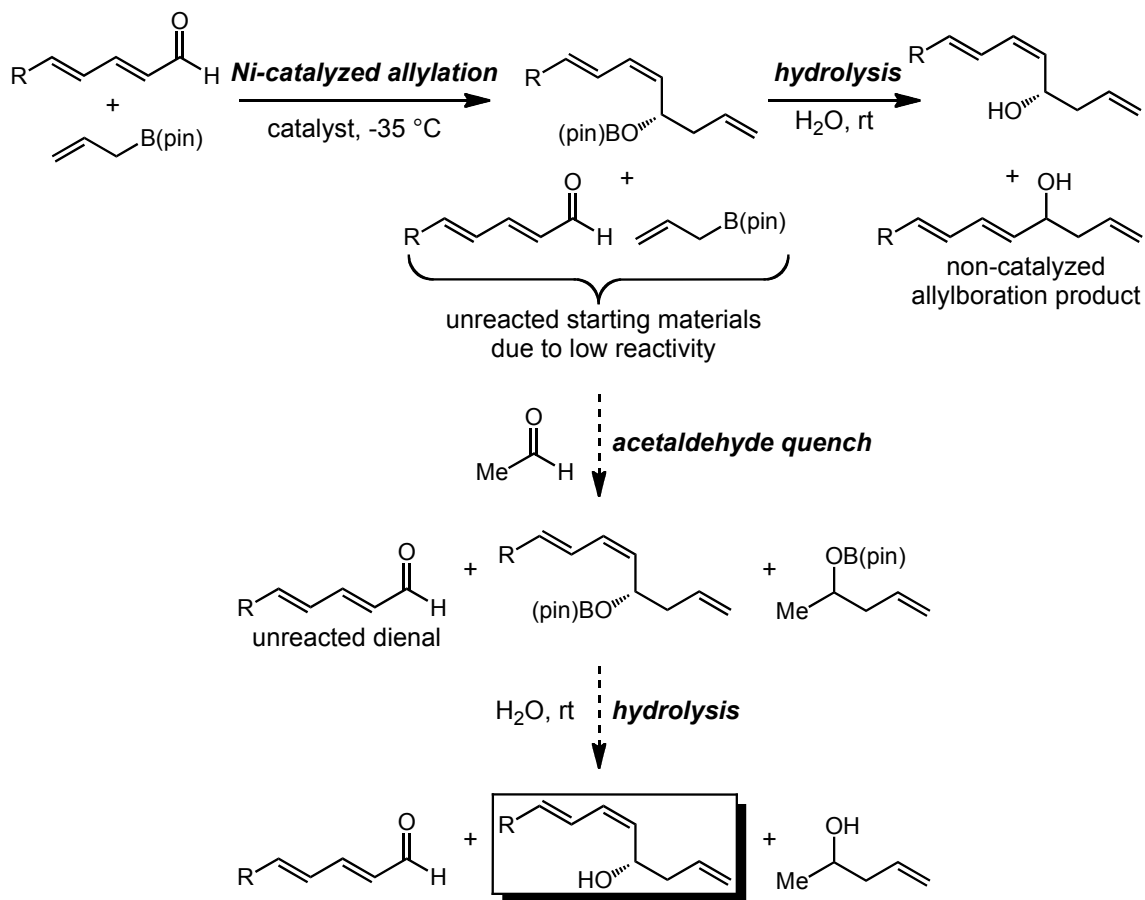
catalyzed process would potentially minimize the formation of *E,E* product. Indeed, when 3 equivalents of allylB(pin) were used in the allylation (vs 1.2 equivalents in Table 1.2), the *E,Z* to *E,E* ratio was increased for both **1.37** and **1.38**. However, since the *E,Z* and *E,E* geometric isomers are inseparable during SiO<sub>2</sub> chromatography (a general phenomenon for all the products), the desired *E,Z* products could not be obtained as single compounds, even though the calculated yields are in the synthetically useful range.

Carefully inspecting Table 1.2 again was informative. If the direct allylboration of the aldehydes produce the *E,E* isomers, believed to occur through 6-membered-ring transition states, why would it become so much faster when oxygen functionalities are present five carbons away on aldehyde substrates? Additionally, at -35 °C, non-catalyzed allylboration of dienals is generally too slow to produce any product.<sup>11</sup> We thus suspected the protected alcohol moieties on the substrate are in fact affecting the reaction rate of the catalyzed process. Based on our mechanistic hypothesis, the intermediates responsible for 1,2-allylation should involve  $\pi$ -allyl ligands on the  $\beta$ -,  $\gamma$ -,  $\delta$ -carbon of the substrates (see **1.V**, Scheme 1.8), which brings the  $\delta$ -carbon close to the metal center. We suspect that oxygen functionalities on substrates might coordinate to Ni center and slow down the reaction. This hypothesis seems reasonable except it does not explain the low *E,Z/E,E* ratio observed. It was then further postulated that the *E,E* products might be formed when the reaction is quenched with water and allowed to warm to room temperature (i.e. allylB(pin) is not destroyed during work-up). (Scheme 1.10)

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<sup>11</sup> For related examples: (a) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868. (b) Roush, W. R.; Walts, A. E. *Tetrahedron Lett.* **1985**, *26*, 3427. (c) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

**Scheme 1.10**



To test the hypothesis, a control experiment was conducted, in which dienals and allylB(pin) were mixed in THF-H<sub>2</sub>O at room temperature, mimicking the reaction condition after quenching. The corresponding *E,E*-allylic alcohol was quickly formed after a short period of time, which supports the plausibility of the above-discussed assumption. Therefore, conditions that accelerate the catalyzed reaction together with effective means to diminish non-catalyzed allylation during work-up should deliver the desired *E,Z* isomers as single products. Consuming unreacted allylB(pin) by adding

acetaldehyde would offer one such method since the alcohol produced can be easily removed by reduced pressure (Scheme 1.10).

As given in Table 1.3, dienals bearing oxygen functionality were treated with extra allylB(pin) in the Ni-catalyze allylation. After 18 hours, the reactions were quenched with a large excess of acetaldehyde, and allowed to stir for another 30 minutes before adding water to hydrolyze the boronic esters to free alcohols. With the new set of conditions, *E,Z/E,E* ratio was significantly improved for the substrates listed below. Remarkably, the most problematic dienal **1.32**, **1.34** was isolated in a 7:1 ratio favoring the *E,Z* product (vs 1:2 under previous condition, entry 6, Table 1.2).

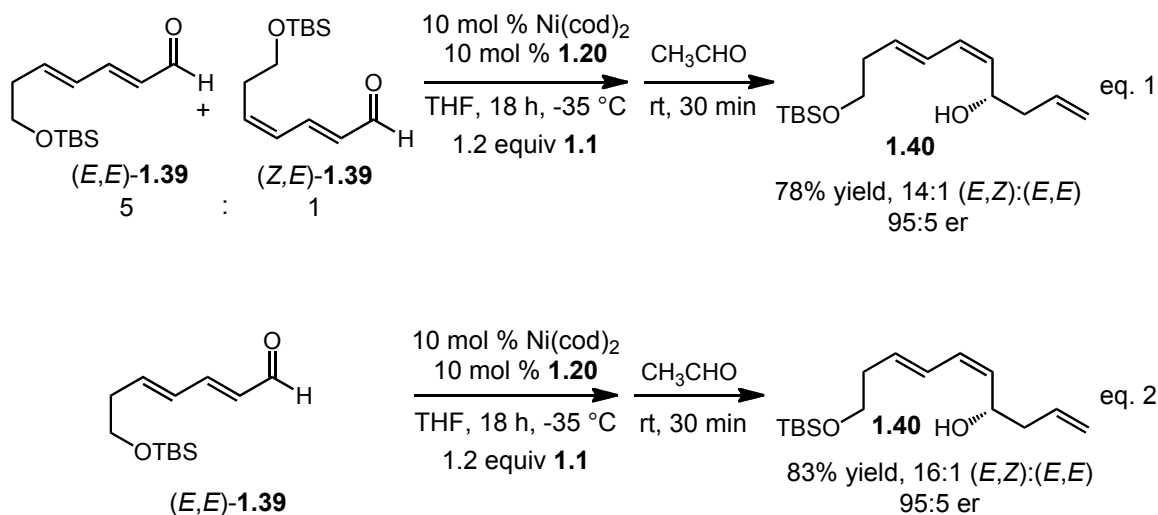
**Table 1.3 Oxygenated Dienals as Substrates**

entry	substrate	product	%yield <sup>a</sup>	( <i>E,Z</i> ):( <i>E,E</i> )	er
1			73	15:1	97:3
2			90	15:1	87:13
3			81	7:1	93:7
4			83	16:1	95:5

<sup>a</sup> Yield refers to the mixture of two isomers if applicable.

During the preparation of  $\delta$ -substituted dienals for Ni-catalyzed allylations, it was difficult to access isomerically pure (*E,E*)-dienals. In fact, the isomeric mixtures are much easier to obtain adopting existing synthetic methodologies such as olefination. According to our initial mechanistic hypothesis, we envisioned that if rapid isomerization of  $\eta^3$ -allyl-Ni(II) happens before the carbon-carbon formation, mixtures of olefin isomers will provide allylation products in the comparable selectivity as obtained from pure substrates. To test this concept, a mixture of (*Z,E*)-**1.39** and (*E,E*)-**1.39** was subjected to the allylation conditions and it was found that the reaction outcome was very similar to that from pure (*E,E*)-**1.39**. If the (*Z,E*)-**1.39** converted to the observed product, this result supports our mechanistic proposal and is of substantial practical importance. (Scheme 1.11)

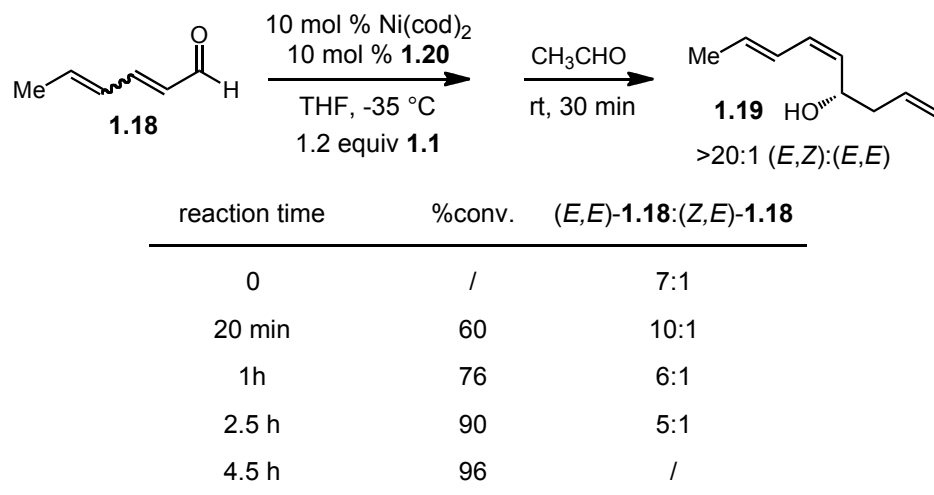
**Scheme 1.11**



The phenomena observed above can be reasoned in an alternate way: the starting dienals undergo Ni-catalyzed isomerization to the thermodynamically more stable (*E,E*)-

**1.39** under Ni-catalysis, which then delivers the product (isomerization before the reaction instead of during the reaction). Since technically now the two reactions share the same substrates, they can afford the same product in similar selectivity. To test this hypothesis, a mixture of (*E,E*)-**1.18** and (*Z,E*)-**1.18** (7:1) was subjected under standard allylation condition. Small portions of the reactions were quenched with acetaldehyde periodically to consume the unreacted allylB(pin) and the remaining starting materials were analyzed by  $^1\text{H}$  NMR to determine the (*E,E*)-**1.18** to (*Z,E*)-**1.18** ratio. The experimental data suggests that the starting material is not rapidly isomerized prior to reaction or else the (*E,E*)-**1.18** should increase over the course of the reaction. Instead, it appears the allylation product is formed directly from both isomers of the dienal. (Scheme 1.12)

**Scheme 1.12**



**C. Synthetic Utility.** As demonstrated above, with the Ni-catalyzed allylation of readily prepared geometric mixtures of dienals, unique *trans,cis*-allylic alcohols can be



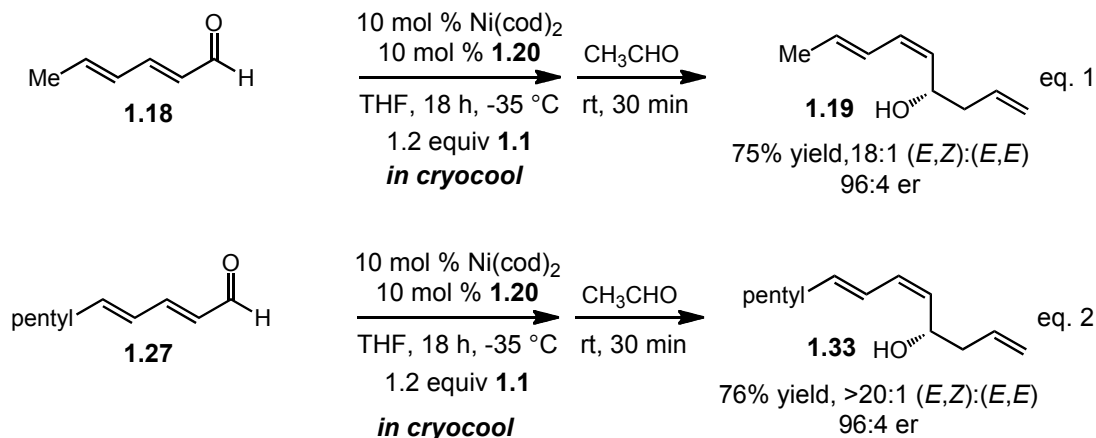
easily accessed in excellent enantiopurity. Manipulating the diene, terminal alkene and/or the tertiary alcohol moiety on these compounds would allow for target-directed synthesis of stereo defined complex molecules.

Before describing the representative examples we have carried out to functionalize the allylic alcohol products, a more practical procedure for the Ni-catalyzed enantioselective allylation of dienals will be presented. In general, the Ni-catalyzed allylations are set up in a -35 °C freezer in a drybox, to ensure an air- and moisture-free environment and for the temperature. However, this method presents a few practical limitations: 1. Not all dryboxes are installed with freezers. 2. The temperature of a drybox freezer is often preset. The use of a freezer is also not practical for large-scale application (gram-scale or larger). Therefore, a more practical method to conduct the reaction is necessary.

Efforts were made to conduct the reaction outside the glovebox through the use of cryocool technology, the temperature of which can easily be manipulated. The primary difficulty encountered in this effort, is that the nickel catalyst (or the reaction itself) is so air- and moisture-sensitive that adding one reagent by syringe outside the glovebox still partially deactivated the catalyst, thereby delivering *E,Z*-allylic alcohols in lower enantioselectivity and with low efficiency. To minimize exposure of the reaction to air and moisture, a strategy was applied in which a large vial containing two smaller ones was utilized as the reaction vessel. AllylB(pin) and the substrate were placed in the small containers, separately; the THF solution of catalyst was placed in the large vial. The vial was sealed, and removed from the glovebox and carefully positioned in the cryocool

(avoid premixing of the three). Once the contents of the vessel were cooled to the desired temperature, it was gently shaken to allow the reagents and catalyst to mix. Through this procedure, the Ni-catalyzed allylation of dienals can proceed outside a drybox which enables the future temperature tuning and broader application (Scheme 1.13).

**Scheme 1.13**



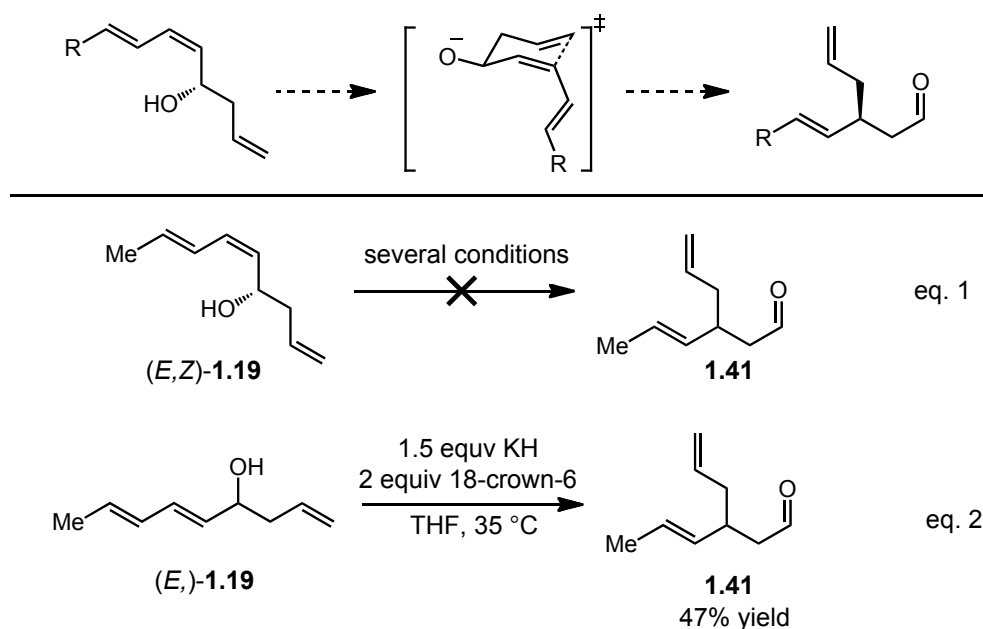
With more practical means to construct the optically pure *trans,cis*-allylic alcohols, several transformations were carried out in order to demonstrate the ease of synthetic manipulations of these compounds.

Since the 1,2-allylation of dienals are perfectly set up for oxy-Cope rearrangement,<sup>12</sup> a panel of conditions was examined aiming to promote the rearrangement of (*E,Z*)-**1.19**. The enantiomerically enriched (*E,Z*)-**1.19** was treated with several bases (KH, NaH, KH with 18-crown-6) and Pd(II) catalyst [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] in different solvents (THF, PhMe, MeCN) and under different temperature (from room

<sup>12</sup> (a) Berson, J. A.; Jones, M. Jr. *J. Am. Chem. Soc.* **1964**, 86, 5019. For an example of oxy-Cope rearrangement of structurally similar alcohol: (b) Nakai, T.; Tomooka, K.; Wei S. *Chem. Lett.* **1991**, 43.

temperature to 150 °C). However, the expected rearrangement product **1.41** was never observed (Scheme 1.14). In contrast, the racemic (*E,E*)-**1.19** underwent this rearrangement smoothly and delivered **1.41** in 47% yield. We suspect under anionic conditions, (*E,Z*)-**1.19** is more likely to undergo 1,5-hydrogen transfer and generate other products than **1.41**.<sup>13</sup>

**Scheme 1.14**

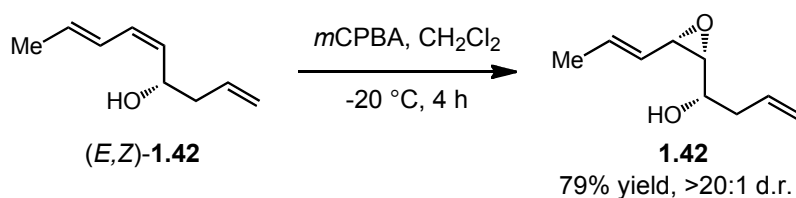


The unique diene pattern present in the allylation products can be used for other synthetic transformations. In general, these transformations are highly diastereoselectivity, delivering stereo defined small molecules whose enantiopurity is originally derived from the Ni-catalyzed allylation. In particular, transformations that

<sup>13</sup> For similar observations: Paquette, L. A.; Crouse G. D.; Sharma A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411.

make use of directing effects<sup>14</sup> and A(1,3) strain<sup>15</sup> as stereocontrol elements can realize selective substrate functionalization. For example, as depicted in Scheme 1.15, these effects lead to selective epoxidation through which (*E,Z*)-**1.19** is efficiently converted into epoxide **1.42** with a high level of stereocontrol.<sup>16</sup> In contrast, the *E*-allylic alcohols are generally much less selective due to the diminished energy difference of the two competing transition states.<sup>8</sup>

**Scheme 1.15**



Richly functionalized epoxide **1.42** can lead to more building blocks that are not easy to access by alternative strategies. For example, ring closing metathesis of **1.42** with the second generation Hoveyda-Grubbs catalyst furnishes novel epoxycyclohexadienol **1.45** (c, Scheme 1.15).<sup>17</sup> The vinyl epoxide moiety in **1.42** is also perfectly set up for Pd-catalyzed 1,4-addition under neutral conditions, wherein pronucleophiles are activated by the epoxide oxygen upon opening. As shown in paths a and b (Scheme 1.16), 1,4-adducts **1.43** and **1.44** are generated as single isomers, with oxygen and carbon nucleophiles respectively.

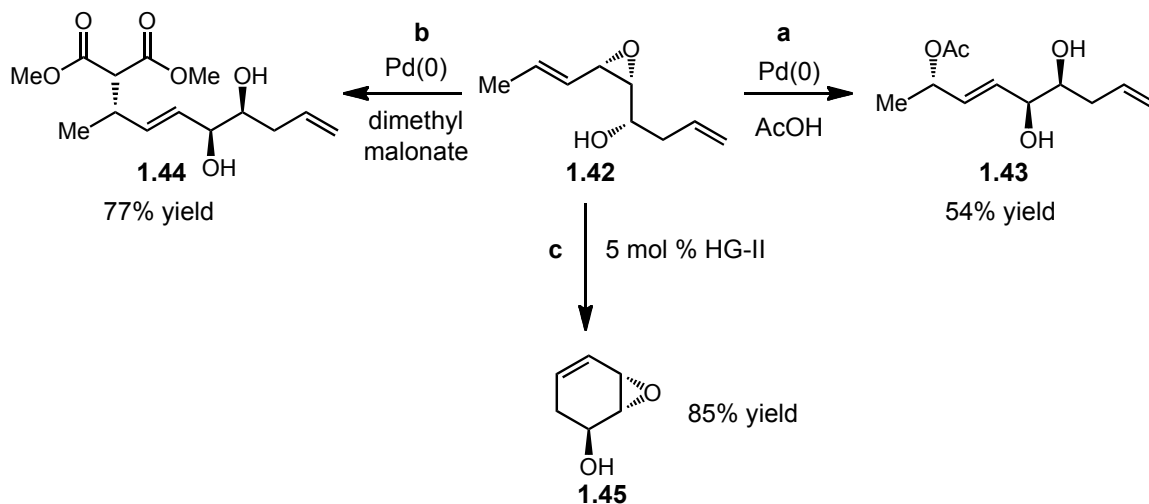
<sup>14</sup> Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307.

<sup>15</sup> Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1941.

<sup>16</sup> (a) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, 96, 5254. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 20, 4733. (c) Yoshida, S.; Asano, M.; Kobayashi, Y. *Tetrahedron Lett.* **2005**, 46, 7243.

<sup>17</sup> Garber, S. B.; Kingbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168.

### Scheme 1.16



## IV. CONCLUSION

A unique catalytic enantioselective allylation of unsaturated carbonyls has been developed. This reaction is catalyzed by Ni/chiral phosphine complexes, likely through the 3,3'-reductive elimination to accomplish the observed olefin isomerization. The functional group pattern that is packaged in the reaction products is relatively unique and has been employed in highly stereoselective synthetic manipulations.

## V. EXPERIMENTAL PROCEDURES

**A. General Information.**  $^1\text{H}$  NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ : 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling

constants (Hz), and assignment.  $^{13}\text{C}$  NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ : 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer,  $\nu_{\text{max}}$   $\text{cm}^{-1}$ . Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed through the use of forced flow (flash chromatography) on silica gel ( $\text{SiO}_2$ , 230 $\times$ 450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25  $\mu\text{m}$  silica gel plates purchased from Silicycle. Visualization was performed through the use of ultraviolet light (254 nm), phosphomolybdic acid (PMA) in ethanol, or potassium permanganate ( $\text{KMnO}_4$ ) in water. Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supleco  $\beta$ -Dex 120 column with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector with methanol as the modifier. Analytical high performance liquid chromatography (HPLC) was performed on a Shimadzu chromatography equipped with two LC-10APvp pumps, SPD-10AVvp UV detector and SIL-10ADvp injector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV polarimeter.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) and dichloromethane (DCM) were purified through the use of a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Bis(1,5-cyclooctadiene)nickel(0) [Ni(cod)<sub>2</sub>] and tricyclohexylphosphine (PCy<sub>3</sub>) were purchased from Strem Chemicals, Inc. Acetic acid and dimethyl malonate were distilled under reduced pressure. Hoveyda-Grubbs catalyst second generation (HG-II) refers to [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(*o*-isopropoxyphenylmethylene)ruthenium.<sup>17</sup> All other reagents were purchased from either Fisher or Aldrich and used without further purification. (*R,R*)-*t*BuTADDOLPPh (**1.3**),<sup>2b</sup> (*R,R*)-TADDOLPPh (**1.20**),<sup>2b</sup> (*R,R*)-xylylTADDOLPPh (**1.21**),<sup>2b</sup> (*R,R*)-TADDOLPN(C<sub>4</sub>H<sub>8</sub>) (**1.22**)<sup>18</sup>, (*R,R*)-TADDOLP(3,5-dimethylphenyl) (**1.23**),<sup>19</sup> (*R,R*)-TADDOLP(2-methylphenyl) (**1.24**),<sup>19</sup> (*R,R*)-TADDOLP(2-naphthyl) (**1.25**)<sup>19</sup> and (*R,R*)-TADDOLPN(C<sub>4</sub>H<sub>8</sub>) (**1.26**)<sup>2b</sup> were prepared according to literature procedures.

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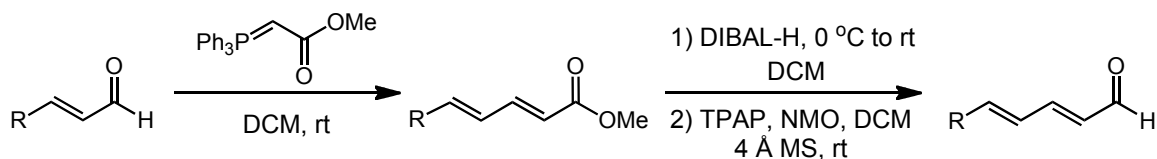
<sup>18</sup> Burks, H. E.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

<sup>19</sup> Burks, H. E. "Transition Metal-Catalyzed Enantioselective Synthesis and Functionalization of 1,2- and 1,4-Bis(boronate)esters". Ph.D. dissertation, Boston College, 2008.

## B. Experimental Procedures.

### 1. Preparation of Dienals

#### Representative Procedure for the Synthesis of Dienals:



The following dienals were prepared from commercially available  $\alpha,\beta$ -unsaturated aldehydes: (2*E*,4*E*)-deca-2,4-dienal (**1.27**)<sup>20</sup> and (2*E*,4*E*)-phenylpenta-2,4-dienal (**1.29**).<sup>21</sup> Spectral data are in accordance with the literature references.

(2*E*,4*E*)-5-Cyclohexylpenta-2,4-dienal (**1.28**) was prepared from (*E*)-3-cyclohexylacrylaldehyde, which was originally synthesized from cyclohexanecarboxaldehyde according to general procedure. Spectral data are in accordance with the literature references.<sup>22</sup>

(2*E*,4*E*)-5-(Furan-2-yl)penta-2,4-dienal (**1.30**) was prepared according to the literature procedure. Spectral data are accordance with the literature references.<sup>23</sup>

<sup>20</sup> Rein, T.; Kann, N.; Åkermærk, B.; Helquist, P. *J. Org. Chem.* **1990**, 55, 5312.

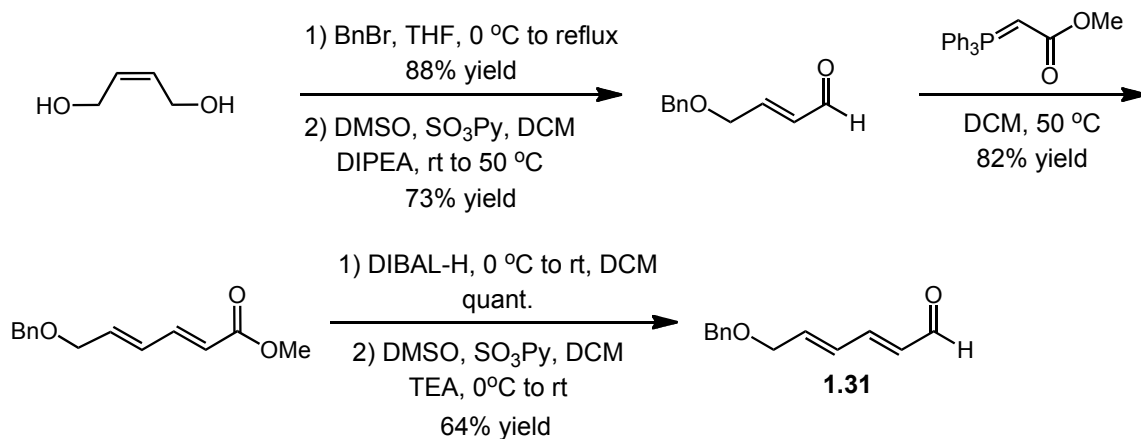
<sup>21</sup> Shi, M.; Tian, G.; Li, J. *Tetrahedron* **2009**, 65, 3404.

<sup>22</sup> Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, 51, 4483.

<sup>23</sup> Bellassoued, M.; Salemkour, M. *Tetrahedron* **1996**, 52, 4507.

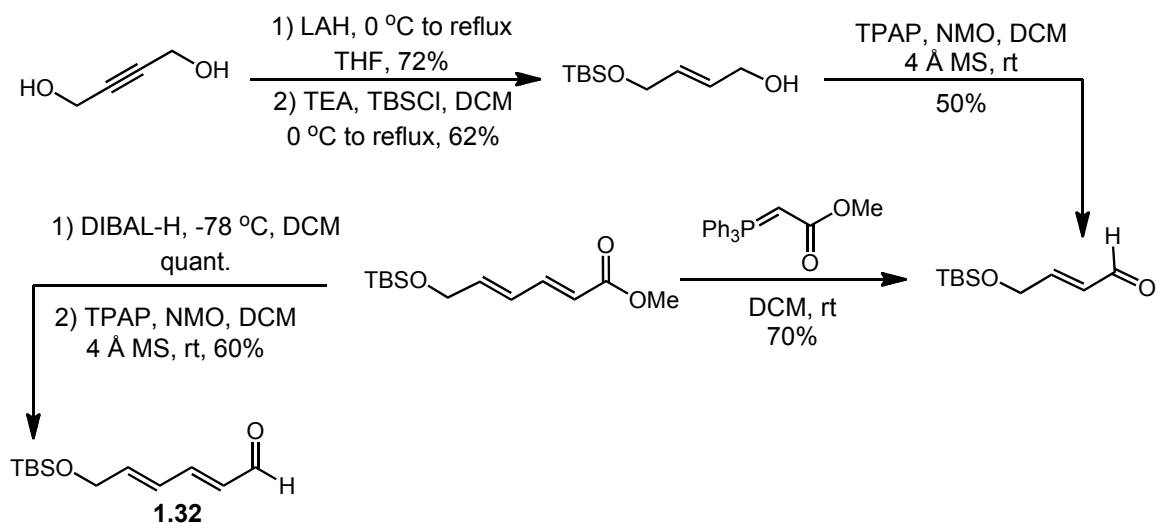


**Preparation of (2E,4E)-6-(benzyloxy)hexa-2,4-dienal:**



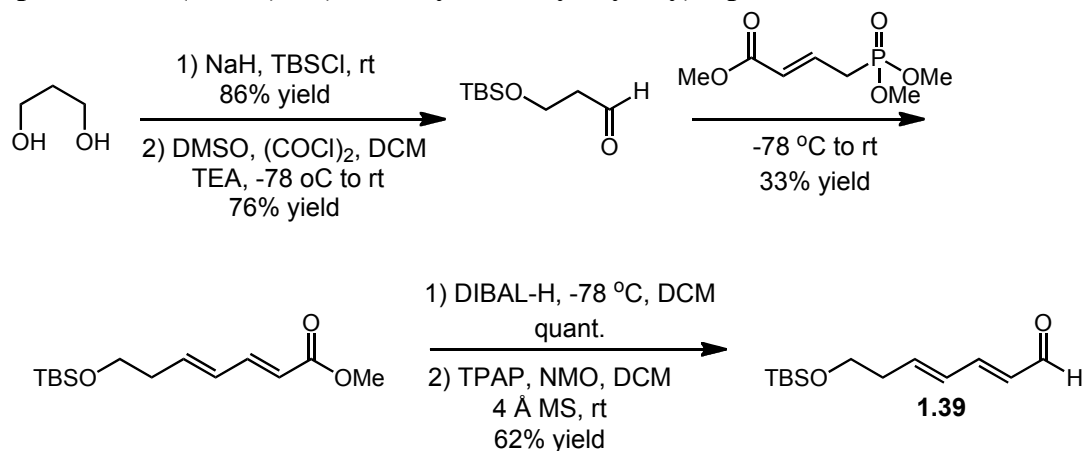
**(2E,4E)-6-(Benzyloxy)hexa-2,4-dienal (1.31).** A yellow oil.  $R_f = 0.37$  (3:1 hexane:EtOAc);  $^1\text{H}$  NMR (400 Hz, CDCl<sub>3</sub>):  $\delta$  4.18 (2H, d,  $J = 5.2$  Hz, OCH<sub>2</sub>CH=CH), 4.57 (2H, s, PhCH<sub>2</sub>O), 6.16 (1H, dd,  $J = 15.2$  Hz, 8.0 Hz, C(O)HCH=CH), 6.32 (1H, dt,  $J = 15.2$  Hz, 5.2 Hz, OCH<sub>2</sub>CH=CH), 6.58 (1H, ddm,  $J = 15.2$  Hz, 10.8 Hz, OCH<sub>2</sub>CH=CH), 7.13 (1H, dd,  $J = 15.4$  Hz, 11.0 Hz, C(O)HCH=CH), 7.31-7.36 (5H, m, Ph-H), 9.58 (1H, d,  $J = 8.0$  Hz, C(O)H);  $^{13}\text{C}$  NMR (125 Hz, CDCl<sub>3</sub>):  $\delta$  194.0, 151.4, 141.2, 137.9, 132.0, 126.2, 128.7, 128.1, 128.0, 73.1, 69.7 ppm; IR (neat): 3030.9 (w), 2845.9 (br), 2735.3 (w), 1678.8 (s), 1643.4 (s), 1602.1(w), 1469.6 (w), 1453.3 (m), 1391.1 (w), 1360.4 (m), 1161.9 (m), 1101.9 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>13</sub>H<sub>15</sub>O<sub>2</sub> [M+H]<sup>+</sup>: calculated 203.1072, found: 203.1082.

**Preparation of (2E,4E)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dienal:**



A light yellow oil.  $R_f = 0.48$  (3:1 hexane:EtOAc);  $^1\text{H}$  NMR (400 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.09 (6H, s,  $\text{Si}(\text{CH}_3)_2$ ), 0.93 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 4.34 (2H, dd,  $J = 4.2$  Hz, 1.8 Hz,  $\text{SiOCH}_2\text{CH}=\text{CH}$ ), 6.15 (1H, dd,  $J = 15.2$  Hz, 8.0 Hz,  $\text{C}(\text{O})\text{HCH}=\text{CH}$ ), 6.32 (1H, dt,  $J = 15.2$  Hz, 4.0 Hz,  $\text{SiOCH}_2\text{CH}=\text{CH}$ ), 6.56 (1H, ddt,  $J = 15.2$  Hz, 10.8 Hz, 2.0 Hz,  $\text{SiOCH}_2\text{CH}=\text{CH}$ ), 7.13 (1H, dd,  $J = 15.4$  Hz, 11.0 Hz,  $\text{C}(\text{O})\text{HCH}=\text{CH}$ ), 9.57 (1H, d,  $J = 8.4$  Hz,  $\text{C}(\text{O})\text{H}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  193.9, 151.7, 144.4, 131.5, 127.0, 63.1, 26.1, 18.7, -5.05 ppm; IR (neat): 2954.7 (m), 2930.0 (m), 2886.1 (w), 2856.8 (w), 2728.7 (m), 1684.6 (s), 1645.7 (s), 1602.7 (w), 1643.4 (w), 1362.1 (w), 1264.2 (m), 1161.5 (m), 1131.98 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{23}\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$ : calculated 227.1467, found: 227.1475.

**Preparation of (2E,4E)-7-(tert-butyldimethylsilyloxy)hepta-2,4-dienal:**



**(2E,4E)-7-(tert-Butyldimethylsilyloxy)hepta-2,4-dienal (1.39).** A yellow oil.  $R_f$  = 0.65 (3:1 hexane:EtOAc);  $^1\text{H}$  NMR

(400 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.05 (6H, s,  $\text{Si}(\text{CH}_3)_2$ ), 0.89 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 2.43 (2H, q,  $J$  = 6.4 Hz,  $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ), 3.73 (2H, t,  $J$  = 6.4 Hz,  $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ), 6.09 (1H, dd,  $J$  = 15.2 Hz, 8.0 Hz,  $\text{C}(\text{O})\text{HCH}=\text{CH}$ ), 6.26-6.41 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}$  and  $\text{CH}_2\text{CH}=\text{CH}$ ), 7.09 (1H, dd,  $J$  = 15.2 Hz, 10.0 Hz,  $\text{C}(\text{O})\text{HCH}=\text{CH}$ ), 9.55 (1H, d,  $J$  = 7.6 Hz,  $\text{C}(\text{O})\text{H}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  194.0, 152.6, 143.7, 130.6, 130.4, 62.1, 36.9, 26.1, 18.6, -5.0 ppm; IR (neat): 2953.4 (m), 2928.7 (m), 2885.7 (w), 2856.8 (m), 2738.5 (w), 1685.1 (s), 1640.9 (s), 1600.3 (w), 1471.1 (w), 1289.1 (w), 1254.8 (m), 1098.7 (s), 936.7 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{25}\text{O}_2\text{Si}$   $[\text{M}+\text{H}]$ : calculated 241.1624, found: 241.1633.

**2. Representative Procedure for Non-Catalyzed Allylation (Scheme 1.9).** An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 33.7 mg (0.351 mmol) of sorbic aldehyde in a dry-box under an argon atmosphere, followed by

0.70 mL of THF and 70.7 mg (0.421 mmol) of allylboronic acid pinacol ester, sequentially. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 15 hours. After this time period, deionized water was added and the mixture was allowed to stir for another 10 minutes. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (×3), and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine (*E,Z*):(*E,E*) ratio.

**3. Representative Procedure for Ni-Catalyzed Allylation at Ambient Temperature (Table 1.1).** An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 9.6 mg (0.0351 mmol) of bis(1,5-cyclooctadiene)nickel, 20.1 mg (0.0351 mmol) of chiral ligand **L3**, and 0.70 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 minutes. Next, 33.7 mg (0.351 mmol) of sorbic aldehyde was added, followed by 70.7 mg (0.421 mmol) of allylboronic acid pinacol ester. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 18 hours. After this time period, deionized water was added and the mixture was allowed to stir for another 10 minutes. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (×3), and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine (*E,Z*):(*E,E*) ratio. Silica gel chromatography (10:1 hexane:EtOAc) afforded 37.0 mg (77%) of a light yellow oil of the allylation product as a mixture of isomers.

#### 4. Representative Procedure for Ni-Catalyzed Allylation at -35 °C:

**In a dry-box freezer (Table 1.2 and 1.3):** An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 9.6 mg (0.0351 mmol) of bis(1,5-cyclooctadiene)nickel, 20.1 mg (0.0351 mmol) of chiral ligand **1.20**, and 0.70 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 minutes. Next, 33.7 mg (0.351 mmol) of sorbic aldehyde was added, and the vial was capped and put into the freezer (temperature: -35 °C) inside the dry-box without stirring. Meanwhile, a syringe containing 70.7 mg (0.421 mmol) of allylboronic acid pinacol ester was put into the same freezer. After 30 minutes, the allylboronic acid pinacol ester was quickly transferred to the reaction vial and the vial resealed. The reaction was kept in the dry-box freezer for 18 hours, and deionized water was added. After stirring for another 10 minutes, the aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (×3), and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine (*E,Z*):(*E,E*) ratio. Silica gel chromatography (10:1 hexane:EtOAc) afforded 27.1 mg (56%) of a light yellow oil of the allylation product as a mixture of isomers.

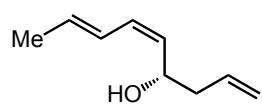
**In a cryocool (Scheme 1.13):** An oven-dried 6-dram vial equipped with a magnetic stir-bar was charged with 9.6 mg (0.035 mmol) of bis(1,5-cyclooctadiene)nickel, 20.1 mg (0.035 mmol) of chiral ligand **1.20**, and 0.70 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 minutes. To a separate oven-dried 1-mL vial was added 33.7 mg (0.351 mmol) of sorbic aldehyde. To a third oven-

dried 1-mL vial was added 117 mg (0.701 mmol) of allylboronic acid pinacol ester. After removal of the magnetic stir-bar from the 6-dram vial, the two uncapped 1-mL vials were transferred carefully into the 6-dram vial without mixing the reaction with the two reagents. The vial was capped, taped with electrical tape, removed from the dry-box, and cooled in a cryocool at -35 °C. After 30 minutes, the vial was gently shaken to mix the contents of the three vials and then put back to the cryocool for another 18 hours. After this time period, 0.6 mL (1.2 mmol) of acetaldehyde was added, followed by warming to ambient temperature over 30 minutes. Deionized water was added, and the mixture was lightly shaken for another 10 minutes. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (×3), and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine (*E,Z*):(*E,E*) ratio. Silica gel chromatography (10:1 hexane:EtOAc) afforded 33.9 mg (70%) of a light yellow oil of the allylation product as a mixture of isomers.

**5. Representative Procedure for the Examination of Dienal Isomerization under Ni-Catalyzed Allylation Condition (Scheme1.12).** An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 28.8 mg (0.105 mmol) of bis(1,5-cyclooctadiene)nickel, 60.3 mg (0.105 mmol) of chiral ligand **1.20**, and 2.1 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 minutes. Next, 101 mg (1.05 mmol) of sorbic aldehyde (7:1 (*E,E*):(*E,Z*)) was added, and the vial was capped and put into the freezer (temperature: -35 °C) inside the dry-box without stirring. Meanwhile, a syringe containing 212 mg (1.26 mmol) of allylboronic acid pinacol ester was put into the same freezer. After 30 minutes, the allylboronic acid

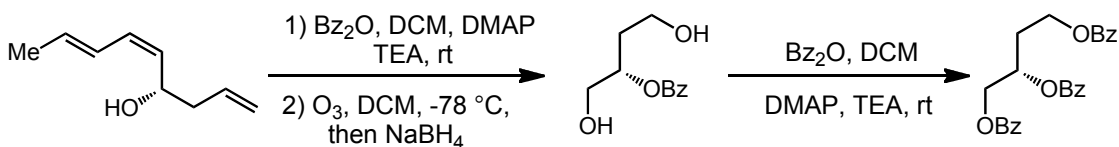
pinacol ester was quickly transferred to the reaction vial and the vial was resealed. After another 20 minutes, 0.2 mL of the reaction mixture was rapidly transferred to a 1-dram vial containing 0.17 mL (0.34 mmol) and equipped with a magnetic stir bar. The vial was allowed to stir and to warm to ambient temperature over 30 minutes. The vial was then removed from the drybox and deionized water was added. After stirring for another 10 minutes, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and the organic layer was filtered through a plug of silica gel and concentrated in *vacuo*. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine (*E,E*):(*Z,E*) ratio of **1.18**, (*E,Z*):(*E,Z*) ratio of **1.19** and conversion. The partial quenching process was repeated at the 1 hour, 2.5 hours and 4.5 hours since the reaction.

## 6. Characterization and Proof of Stereochemistry


**(*S,5Z,7E*)-Nona-1,5,7-trien-4-ol (1.19).** <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>): δ 1.60 (1H, d, *J* = 3.6 Hz, OH), 1.79 (3H, dd, *J* = 6.4 Hz, 1.6 Hz, CH<sub>3</sub>), 2.32 (2H, ddt, *J* = 6.8, 6.0, 1.2 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.63 (1H, dddd, *J* = 8.8, 6.0, 6.0, 3.2 Hz, CHOH), 5.12-5.18 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.30 (1H, dd, *J* = 10.8, 8.8 Hz, CH=CHCHOH), 5.73-5.88 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub> and CH<sub>3</sub>CH=CH), 6.04 (1H, dd, *J* = 11.2, 10.8 Hz, CH=CHCHOH), 6.35 (1H, ddq, *J* = 14.8, 11.4, 1.2 Hz, CH<sub>3</sub>CH=CH); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 134.3, 132.1, 130.7, 130.4, 126.6, 118.3, 67.3, 42.3, 18.5 ppm; IR (neat): 3349.4 (br), 3076.5 (w), 3021.8 (m), 2978.7 (w), 2914.2 (m), 2852.4 (m), 1654.9 (m), 1641.0 (m), 1433.7 (m), 1376.2 (m), 1306.3 (m), 1019.6 (s), 982.2 (s), 946.3 (s), 912.7 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>9</sub>H<sub>13</sub> [M+H-H<sub>2</sub>O]: calculated 121.1017, found:

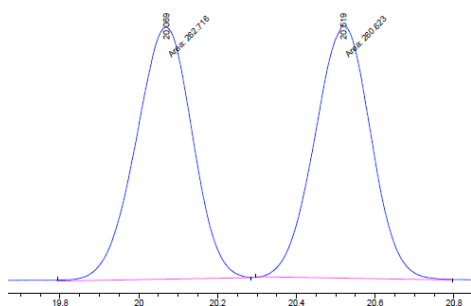
121.1017;  $[\alpha]_D^{20} = -2.3$  ( $c = 0.42$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a light yellow oil (40.1 mg, 84% yield).  $R_f = 0.42$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison of the acylated product with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. Absolute stereochemistry was determined by converting the allylation product to benzoate, followed by ozonolysis/reduction, and converting the corresponding diol to tribenzoate, as shown bellow. The resulting tribenzoate was compared on chiral SFC to butane-1,2,4-triyl tribenzoate and (*S*)- butane-1,2,4-triyl tribenzoate which were derived from commercially available butane-1,2,4-triol and (*S*)-1,2,4-triol respectively.

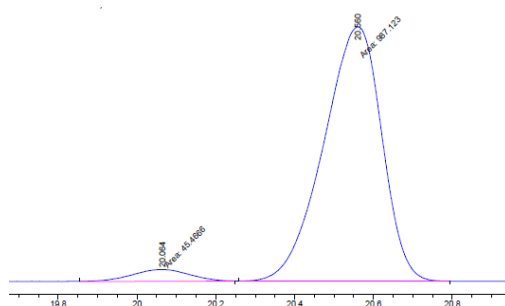




*Chiral GLC ( $\beta$ -dex, supelco, 100 °C, 20 psi) - analysis of the acetate of (5Z,7E)-nona-1,5,7-trien-4-ol.*



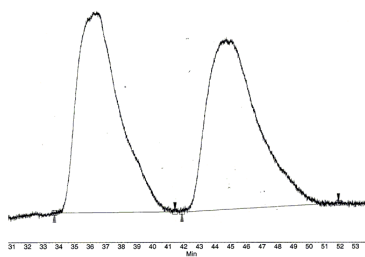
racemic



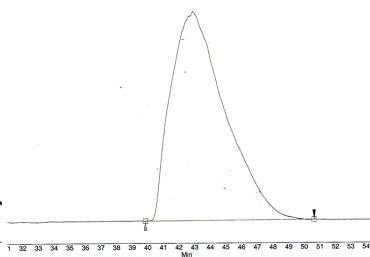
allylation product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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2	20.560	MM	0.1709	987.12329	96.24561	95.59684

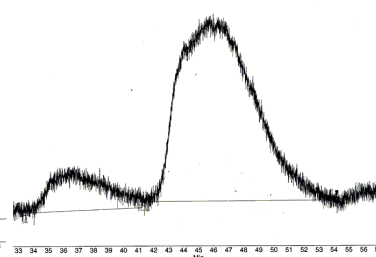
*Chiral SFC (OD-H, Chiralpak, 220 nm, 3.0 mL/min, 3.0% MeOH, 150 psi, 50 °C) – analysis of butane-1,2,4-triyl tribenzoate.*



racemic tribenzoate



S-tribenzoate



tribenzoate derived from allylation product

S-tribenzoate

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
39.85	42.90	50.63	0.00	100.00	7144.1	28677.1	100.000
				100.00	7144.1	28677.1	100.000

tribenzoate derived from allylation product

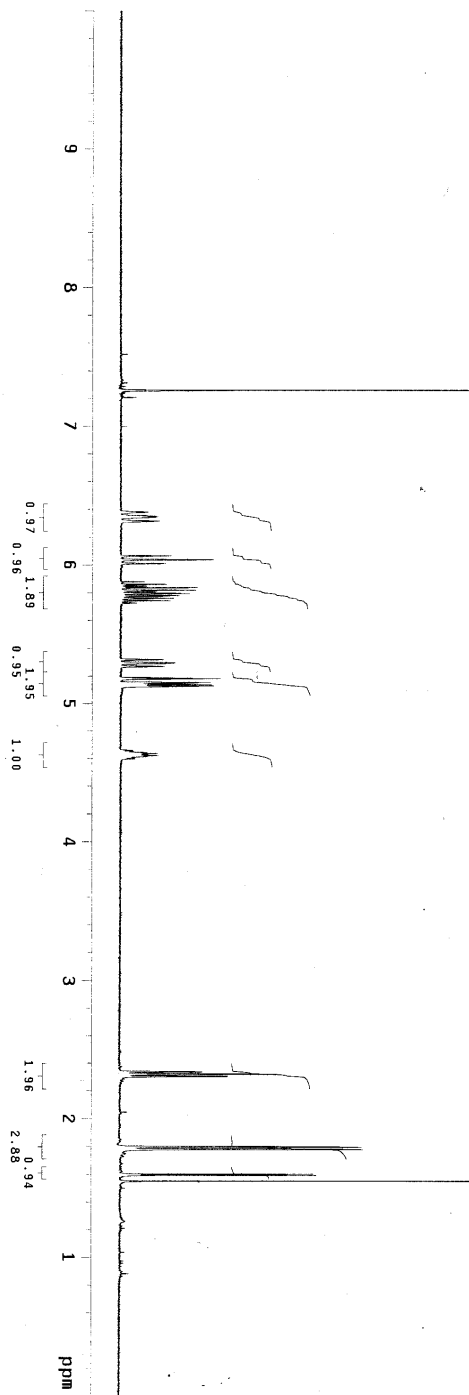
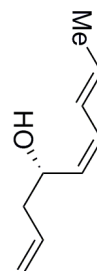
Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
33.50	36.39	41.24	0.00	14.00	64.1	273.1	14.001
41.62	45.73	54.18	0.00	86.00	292.2	1677.2	85.999
				100.00	356.3	1950.3	100.000

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P2-3-178-P

exp5 std1h

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file	exp	dpr	30
ACQUISITION	exp	dof	0
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in	H1	dmf	200
at	3.000	wtfile	ft
sw	35992	proc	not used
nb	5998.8	ft	
td	3400	tn	
tdwf	63	weff	
pw	7.1	wexp	
di	2.000	wbs	
to	0	wnt	
nt	32		
st	32		
aflock	not used		
gain	not used		
fl	not used		
in	n		
dp	y		
display	-0.1		
sp	4000.2		
vs	210		
sc	250		
mcmm	16.30		
is	6037.35		
rfl	3902.8		
rft	2904.2		
th	20		
ms	1.000		
ph			



PZ-3-147-PP-C13  
PZ-3-147-PP-C13

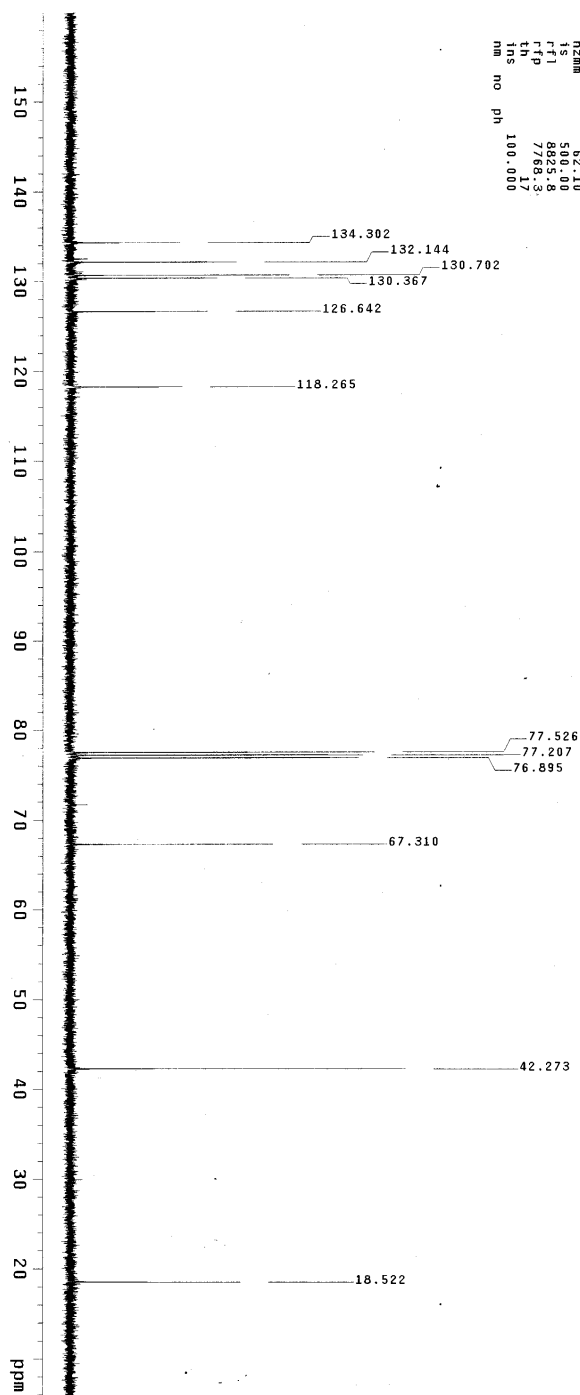
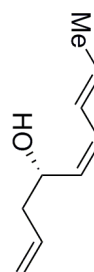
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exp1 std13c
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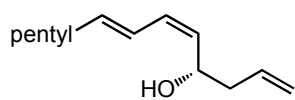
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acquisition    exp      dr      45
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t1         C13         dfm      w
at         0.640       dmf      w
ap         32876       wttle    w
sw         25683.4     wttle    w
bs         1424.4      fn      not used
ss         4           ft      not used
tpwr       55
d1         9.0 weff
dl         4.00 wepd
tof        2211.7 wds
rt         1600      wnt
ct         2.00      wnt
gain       62 n
alock      2 n
gain       2 n
flags      not used

1 l      n
1 n      n
1 n      n
dp DISPLAY y
sp 561.9
wp 1552.3
ss 60
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th 17
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nm nm ph

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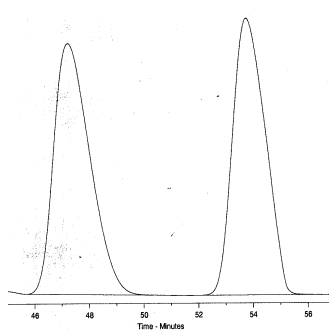
**(*S,5Z,7E*)-Trideca-1,5,7-trien-4-ol (1.33).**  $R_f = 0.59$  (3:1

hexane:EtOAc);  $^1\text{H}$  NMR (400 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.88 (3H, t,  $J =$

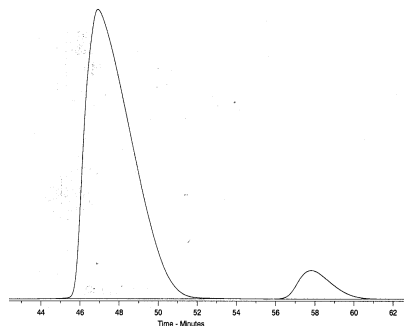
6.8 Hz,  $\text{CH}_3$ ), 1.26-1.41 (6H, m,  $\text{CH}_3(\text{CH}_2)_3$ ), 1.71 (1H, s, OH), 2.10 (2H, q,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}$ ), 2.32 (2H, t,  $J = 6.8$  Hz,  $\text{CH}_2\text{CHOH}$ ), 4.62 (1H, dt,  $J = 8.0, 6.4$  Hz,  $\text{CHOH}$ ), 5.11-5.17 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.30 (1H, dd,  $J = 10.4, 9.2$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.71-5.87 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  and  $\text{CH}_2\text{CH}=\text{CH}$ ), 6.03 (1H, t,  $J = 11.0$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 6.31 (1H, ddt,  $J = 14.8, 11.2, 0.8$  Hz,  $\text{CH}_2\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  137.8, 134.3, 130.9, 130.5, 125.2, 118.3, 67.3, 42.3, 33.0, 31.7, 29.1, 22.7, 14.3 ppm; IR (neat): 3367.7 (br), 3076.4 (m), 2956.4 (s), 2925.4 (m), 2856.7 (m), 1692.3 (m), 1641.0 (m), 1458.8 (m), 1433.1 (m), 1378.4 (m), 1307.7 (m), 1021.2 (s), 984.4 (s), 946.9 (s), 912.2 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{21}$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated 177.1643, found: 177.1639;  $[\alpha]_D^{20} = -1.20$  ( $c = 1.41$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a colorless oil (51.8 mg, 76% yield).  $R_f = 0.59$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. Absolute stereochemistry was determined by converting the allylation product to butane-1,2,4-triyl tribenzoate as described for (*S,5Z,7E*)-nona-1,5,7-trien-4-ol. The resulting tribenzoate was compared on chiral SFC to butane-1,2,4-triyl tribenzoate and (*S*)-butane-1,2,4-triyl tribenzoate derived from commercially available butane-1,2,4-triol and (*S*)-1,2,4-triol, respectively.

*Chiral HPLC (AS, Chiralcel, 0.5 mL/min, 0% Isopropanol, 220 nm) – analysis of (5Z,7E)-trideca-1,5,7-trien-4-ol.*



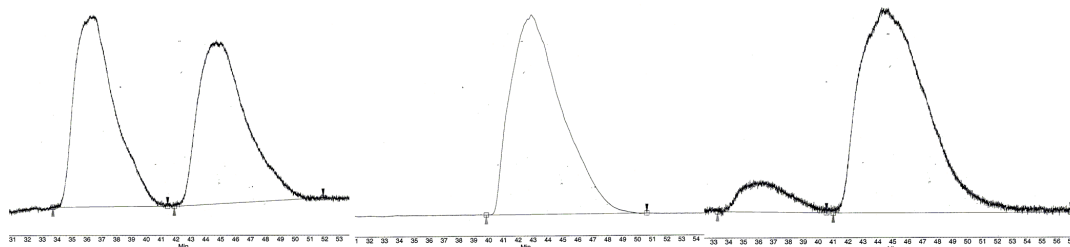
Racemic



allylation product

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	46.94		0.00	N/A	100919500	93.288	BB	2.64
2	57.83		0.00	N/A	7261621	6.712	BB	1.88

*Chiral SFC (OD-H, Chiralpak, 220 nm, 3.0 mL/min, 3.0% MeOH, 150 psi, 50 °C) – analysis of butane-1,2,4-triyl tribenzoate.*



racemic tribenzoate

S-tribenzoate

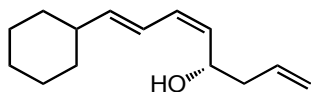
tribenzoate derived from  
allylation product

*S*-tribenzoate

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[ $\mu$ V]	[ $\mu$ V.Min]	[%]
39.85	42.90	50.63	0.00	100.00	7144.1	28677.1	100.000
				100.00	7144.1	28677.1	100.000

tribenzoate derived from allylation product

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[ $\mu$ V]	[ $\mu$ V.Min]	[%]
33.25	35.94	40.55	0.00	9.83	130.9	516.3	9.829
41.01	44.37	56.98	0.00	90.17	903.5	4736.3	90.171
				100.00	1034.4	5252.6	100.000



**(*S,5Z,7E*)-8-Cyclohexylocta-1,5,7-trien-4-ol (1.34).**  $^1\text{H}$  NMR

(400 Hz,  $\text{CDCl}_3$ ):  $\delta$  1.05–1.74 (11H, m,  $(\text{CH}_2)_5$  and OH), 2.03

(1H, dtt,  $J = 7.6, 7.2, 3.6$  Hz,  $\text{CHCH}=\text{CH}$ ), 2.32 (2H, t,  $J = 6.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.63

(1H, dddd,  $J = 8.8, 6.4, 6.0, 2.4$  Hz,  $\text{CHOH}$ ), 5.11–5.18 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.31 (1H,

dd,  $J = 10.0, 8.8$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.70 (1H, dd,  $J = 15.2, 7.2$  Hz,  $\text{CHCH}=\text{CH}$ ), 5.83

(1H, ddt,  $J = 17.2, 10.0, 7.2$  Hz,  $\text{CHCH}=\text{CH}_2$ ), 6.03 (1H, dd,  $J = 11.2, 10.8$  Hz,

$\text{CH}=\text{CHCHOH}$ ), 6.27 (1H, ddt,  $J = 15.2, 11.2, 0.8$  Hz,  $\text{CHCH}=\text{CH}$ ) ppm;  $^{13}\text{C}$  NMR (100

Hz,  $\text{CDCl}_3$ ):  $\delta$  143.4, 134.4, 131.2, 130.7, 122.7, 118.3, 67.4, 42.3, 41.2, 33.02, 32.99,

26.4, 26.2 ppm; IR (neat): 3338.5 (br), 3075.3 (w), 3008.0 (w), 2978.6 (w), 2921.9 (s).

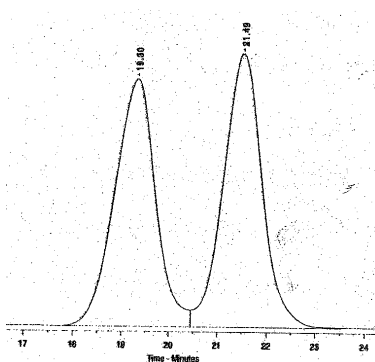
2850.1 (s), 1641.2 (m), 1447.5 (m), 1349.3 (br), 1020.2 (s), 984.0 (s), 947.5 (s), 921.1 (s),

839.9 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{21}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]$ : calculated 189.1643, found:

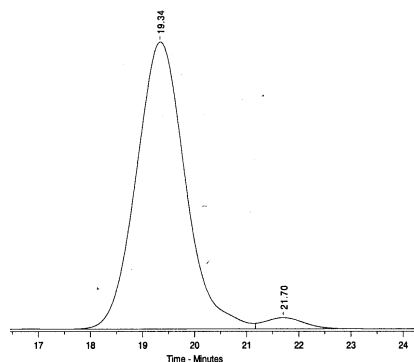
189.1639;  $[\alpha]_D^{20} = -0.91$  ( $c = 1.24$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a light yellow oil (66.5 mg, 92% yield).  $R_f = 0.43$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. The absolute stereochemistry was assigned by analogy.

*Chiral HPLC (AS, Chiralcel, 220 nm, 0.5 mL/min, 0.5% Isopropanol) – analysis of (5Z,7E)-8-cyclohexylocta-1,5,7-trien-4-ol.*



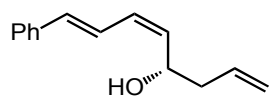
racemic



allylation product

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	19.34		0.00	N/A	41412050	97.035	BV	0.99
2	21.70		0.00	N/A	1265217	2.965	VB	0.92

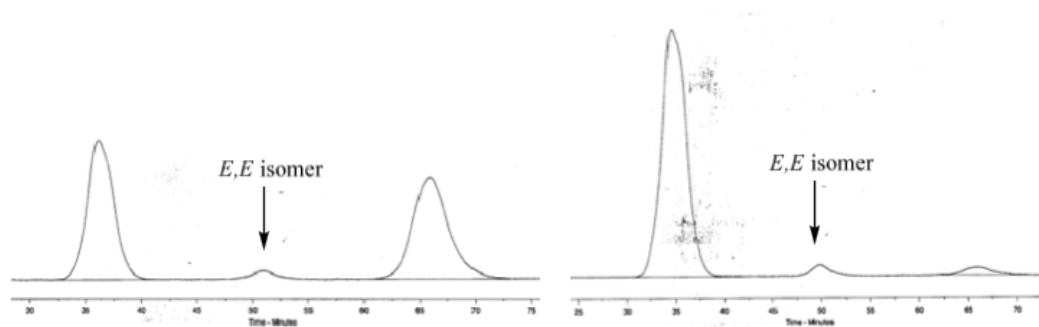




**(*S,5Z,7E*)-8-Phenylocta-1,5,7-trien-4-ol (1.35).**  $^1\text{H}$  NMR (400 Hz,  $\text{CDCl}_3$ ):  $\delta$  1.87 (1H, s, OH), 2.38 (2H, t,  $J = 6.8$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.76 (1H, dt,  $J = 8.0, 6.8$  Hz, CHOH), 5.14-5.21 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.51 (1H, dd,  $J = 10.8, 8.8$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.85 (1H, ddt,  $J = 17.2, 10.0, 7.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.24 (1H, t,  $J = 11.2$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 6.59 (1H, d,  $J = 15.2$ ,  $\text{PhCH}=\text{CH}$ ), 7.07 (1H, dd,  $J = 15.6, 11.2$  Hz,  $\text{PhCH}=\text{CH}$ ), 7.25 (1H, t,  $J = 7.2$  Hz, para-Ph-H), 7.33 (2H, dd,  $J = 8.0, 7.2$  Hz, meta-Ph-H), 7.42 (2H, dd,  $J = 8.0, 0.8$  Hz, ortho-Ph-H);  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  137.1, 134.6, 134.1, 133.3, 130.6, 128.8, 128.0, 128.6, 123.8, 118.5, 67.5, 42.3 ppm; IR (neat): 3361.3 (br), 3077.1 (m), 3027.4 (m), 2978.4 (m), 2906.9 (m), 1638.9 (m), 1597.4 (w), 1493.4 (m), 1448.8 (m), 1306.3 (m), 989.2 (s), 946.1 (s), 916.2 (s), 858.4 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{15}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]$ : calculated 183.1174, found: 183.1177;  $[\alpha]_D^{20} = +3.22$  ( $c = 1.41$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford yellow oil (46.3 mg, 66% yield).  $R_f = 0.33$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. Absolute stereochemistry was determined by converting the allylation product to butane-1,2,4-triyl tribenzoate as described for (*S,5Z,7E*)-nona-1,5,7-trien-4-ol. The resulting tribenzoate was compared on chiral SFC to butane-1,2,4-triyl tribenzoate and (*S*)-butane-1,2,4-triyl tribenzoate derived from commercially available butane-1,2,4-triol and (*S*)-1,2,4-triol, respectively.

Chiral HPLC (OD, Chiralcel, 1.0 mL/min, 1.0% Isopropanol, 220 nm) – analysis of (5Z,7E)-8-phenylocta-1,5,7-trien-4-ol.

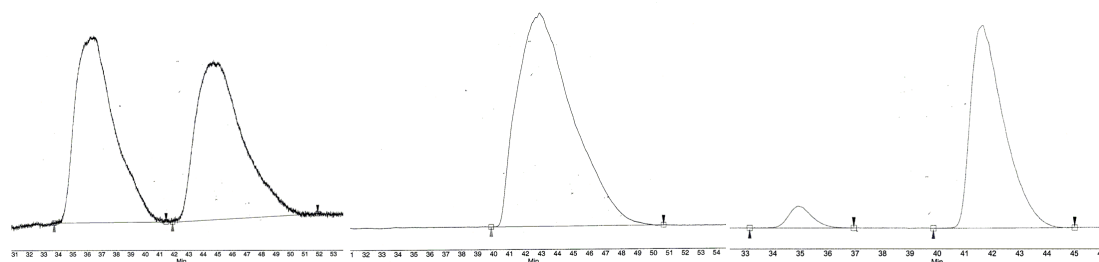


racemic

allylation product

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	34.73		0.00	N/A	9043018	96.063	BB	2.68
2	65.83		0.00	N/A	370651	3.937	BB	3.31

Chiral SFC (OD-H, Chiralpak, 220 nm, 3.0 mL/min, 3.0% MeOH, 150 psi, 50 °C) – analysis of butane-1,2,4-triyl tribenzoate.



racemic tribenzoate

S-tribenzoate

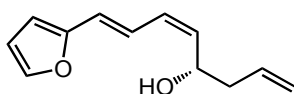
tribenzoate derived from  
allylation product

S-tribenzoate

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
39.85	42.90	50.63	0.00	100.00	7144.1	28677.1	100.000
				100.00	7144.1	28677.1	100.000

tribenzoate derived from allylation product

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[ $\mu$ V]	[ $\mu$ V.Min]	[%]
33.16	34.93	36.96	0.00	7.02	157.6	156.7	7.025
39.86	41.67	45.01	0.00	92.98	1470.5	2074.2	92.975
				100.00	1628.2	2231.0	100.000



(*S,5Z,7E*)-8-(Furan-2-yl)octa-1,5,7-trien-4-ol (**1.36**).  $^1\text{H}$  NMR

(400Hz,  $\text{CDCl}_3$ ):  $\delta$  1.76 (1H, d,  $J = 3.2$  Hz, OH), 2.36 (2H, ddt,

$J = 7.2, 6.4, 1.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.75 (1H, dddd,  $J = 9.6, 6.4, 6.0, 3.2$  Hz,  $\text{CHOH}$ ),

5.13-5.21 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.49 (1H, dd,  $J = 10.0, 9.6$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.85

(1H, ddt,  $J = 17.2, 10.4, 7.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.16 (1H, ddt,  $J = 12.0, 10.4, 0.8$  Hz,

$\text{CH}=\text{CHCHOH}$ ), 6.29-6.40 (3H, m,  $\text{ArCH}=\text{CH}$ , *ortho*-H-Ar and *meta*-H-Ar), 6.96 (1H,

dd,  $J = 15.6, 11.6$  Hz,  $\text{ArCH}=\text{CH}$ ), 7.38 (1H, d,  $J = 1.6$  Hz, *para*-H-Ar);  $^{13}\text{C}$  NMR (100

Hz,  $\text{CDCl}_3$ ):

$\delta$  153.1, 142.6, 134.2, 133.6, 130.2, 122.4, 122.0, 118.6, 111.9, 109.4, 67.4, 42.3 ppm; IR

(neat): 3381.7 (br), 3118.2 (w), 3076.0 (w), 3010.9 (m), 2978.2 (w), 2929.4 (m), 1676.1

(w), 1638.5 (m), 1609.6 (w), 1483.7 (m), 1152.1 (m) 1014.4 (s), 984.1 (s), 942.4 (s),

925.2 (s), 735.8 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{13}\text{O}$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated 173.0966,

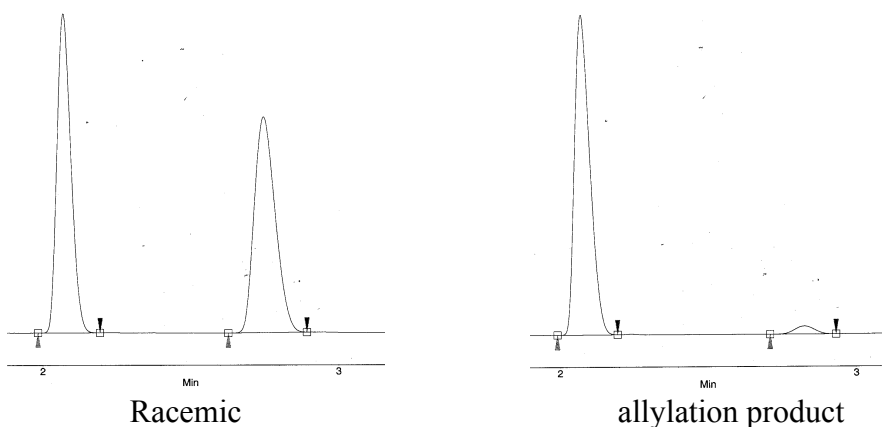
found: 173.0971;  $[\alpha]_{\text{D}}^{20} = 0.65$  ( $c = 1.12$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was

purified on silica gel to afford a yellow oil (48.7 mg, 73% yield) as a *E,Z* and *E,E* mixture

(15:1).  $R_f = 0.28$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. The absolute stereochemistry was assigned by analogy.

*Chiral SFC (AD-H, Chiralpak, 220 nm, 5.0 mL/min, 5.0% MeOH, 150 psi, 50 °C) – analysis of (5Z,7E)-8-(furan-2-yl)octa-1,5,7-trien-4-ol.*



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	1.99	2.07	2.19	0.00	96.87	32872.4	1966.2	96.873
2	UNKNOWN	2.71	2.82	2.93	0.00	3.13	820.9	63.5	3.127
Total						100.00	33693.3	2029.7	100.000

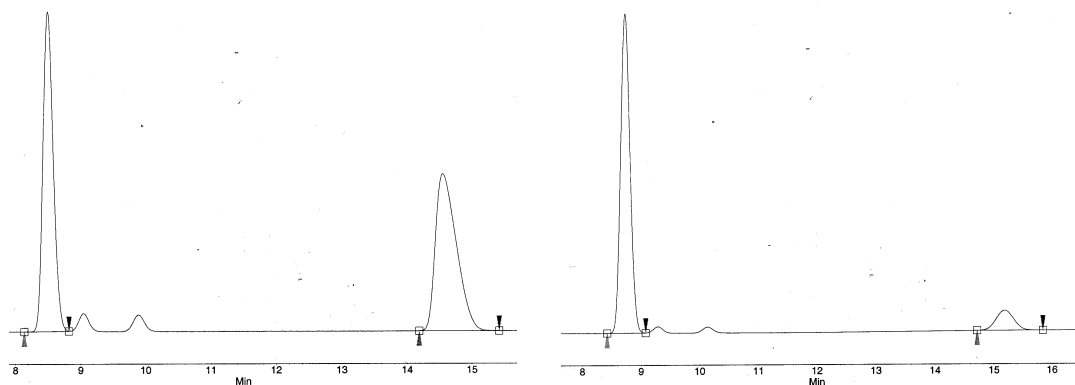

**(S,5Z,7E)-9-(Benzyloxy)nona-1,5,7-trien-4-ol (1.37).** <sup>1</sup>H

NMR (500 Hz, CDCl<sub>3</sub>): δ 1.67 (1H, d, *J* = 2.5 Hz, OH), 2.32 (2H, tt, *J* = 7.0, 0.5 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.09 (2H, d, *J* = 4.5 Hz, OCH<sub>2</sub>CH=CH), 4.53 (1H, s, PhCH<sub>2</sub>O), 4.63 (1H, m, CHOH), 5.13-5.18 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.44 (1H, dd, *J* = 10.5, 9.5 Hz, CH=CHCHOH), 5.77-5.88 (2H, m, OCH<sub>2</sub>CH=CH and CH<sub>2</sub>CH=CH<sub>2</sub>), 6.09

(1H, t,  $J = 11.5$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 6.58 (1H, ddd,  $J = 15.5, 12.0, 1.5$  Hz,  $\text{OCH}_2\text{CH}=\text{CH}$ ), 7.28-7.36 (5H, m, Ar-H);  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  138.3, 134.1, 133.3, 132.2, 129.8, 128.6, 180.0, 127.9, 127.4, 118.6, 72.5, 70.4, 67.2, 42.2 ppm; IR (neat): 3390.1 (br), 3066.2 (m), 3027.8 (m), 292.8 (m), 2853.4 (m), 1640.5 (m), 143.8 (m), 1358.5 (m), 1305.9 (w), 1206.6 (w), 1102.2 (s), 1046.5 (s), 1027.1 (s), 989.5 (s), 915.6 (s), 737.5 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{16}\text{H}_{19}\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]$ : calculated 227.1436, found: 227.1438;  $[\alpha]_{\text{D}}^{20} = -4.3$  ( $c = 0.66$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a yellow oil (77.1 mg, 90% yield) as a *E,Z* and *E,E* mixture (18:1).  $R_f = 0.24$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. The absolute stereochemistry was assigned by analogy.

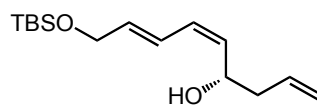
Chiral SFC (AD-H, Chiralpak, 220 nm, 3.0 mL/min, 3.0% MeOH, 150 psi, 50 °C) – analysis of (5Z,7E)-9-(benzyloxy)nona-1,5,7-trien-4-ol.



racemic

allylation product

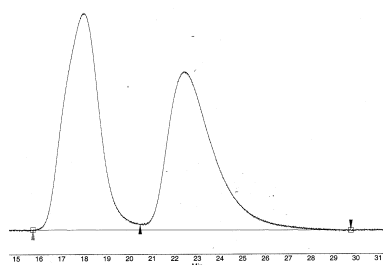
Index	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [μV]	Area [μV.Min]	Area [%]
1	UNKNOWN	8.42	8.73	9.08	0.00	89.43	11834.1	2205.7	89.426
2	UNKNOWN	14.71	15.18	15.84	0.00	10.57	733.2	260.8	10.574
Total						100.00	12567.3	2466.5	100.000


**(S,5Z,7E)-9-(tert-Butyldimethylsilyloxy)nona-1,5,7-trien-4-ol (1.38).** <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>): δ 0.08 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), 0.92 (1H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.63 (1H, d, *J* = 3.2 Hz, OH), 2.32 (2H, t, *J* = 6.8 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.24 (2H, dd, *J* = 4.4, 1.6 Hz, SiOCH<sub>2</sub>CH=CH), 4.64 (1H, dddd, *J* = 8.8, 6.4, 6.0, 2.4 Hz, CHOH), 5.12-5.18 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.40 (1H, dd, *J* = 10.8, 8.8 Hz, CH=CHCHOH), 5.76-5.86 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub> and SiOCH<sub>2</sub>CH=CH), 6.08 (1H,

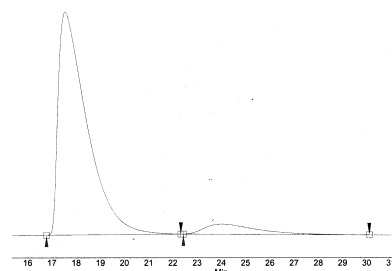
dd,  $J = 11.2, 10.8$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 6.54 (1H, ddq,  $J = 14.0, 11.2, 1.2$  Hz,  $\text{SiOCH}_2\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR (100Hz,  $\text{CDCl}_3$ ):  $\delta$  135.2, 134.2, 132.5, 129.8, 124.4, 118.4, 67.5, 63.5, 42.3, 26.2, 18.7, -4.93, -4.94 ppm; IR (neat): 3380.1 (br), 3077.2 (w), 3009.9 (m), 2954.4 (m), 2895.7 (m), 2856.4 (m), 1641.2 (w), 1471.5 (m), 1362.4 (m), 1253.7 (m), 1100.9 (br), 1007.2 (br), 831.9 (s), 744.2 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{27}\text{OSi}$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated 251.1831, found: 251.1821;  $[\alpha]_{\text{D}}^{20} = -5.9$  ( $c = 0.83$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a light yellow oil (94.9 mg, 81% yield) as a *E,Z* and *E,E* mixture (7:1).  $R_f = 0.43$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. Absolute stereochemistry was determined by converting the allylation product to butane-1,2,4-triyl tribenzoate as described for (*S*,5*Z*,7*E*)-nona-1,5,7-trien-4-ol. The resulting tribenzoate was compared on chiral SFC to butane-1,2,4-triyl tribenzoate and (*S*)- butane-1,2,4-triyl tribenzoate derived from commercial available butane-1,2,4-triol and (*S*)-1,2,4-triol, respectively.

*Chiral SFC (AD-H, Chiralpak, 220 nm, 1.0 mL/min, 1.5% MeOH, 150 psi, 50 °C) – analysis of (S,5Z,7E)-9-(tert-butyltrimethylsilyloxy)nona-1,5,7-trien-4-ol.*



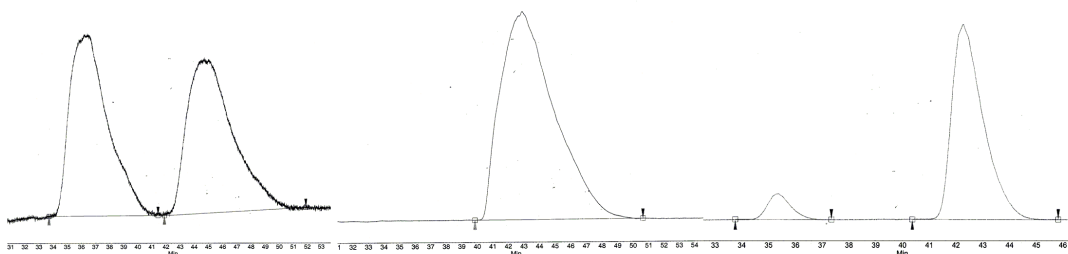
racemic



allylation product

Index	Name	Time			RT Offset	Quantity	Height	Area	
		[Min]	[Min]	[Min]				[μV.Min]	[%]
1	UNKNOWN	16.79	17.55	22.33	0.00	92.41	5295.4	7256.0	92.408
2	UNKNOWN	22.43	24.04	30.11	0.00	7.59	240.4	596.1	7.592
Total						100.00	5535.8	7852.1	100.000

*Chiral SFC (OD-H, Chiralpak, 220 nm, 3.0 mL/min, 3.0% MeOH, 150 psi, 50 °C) – analysis of butane-1,2,4-triyl tribenzoate .*



racemic tribenzoate

S-tribenzoate

tribenzoate derived from  
allylation product

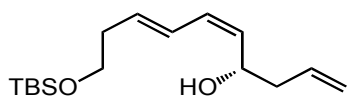
S-tribenzoate

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
39.85	42.90	50.63	0.00	100.00	7144.1	28677.1	100.000
				100.00	7144.1	28677.1	100.000



tribenzoate derived from allylation product

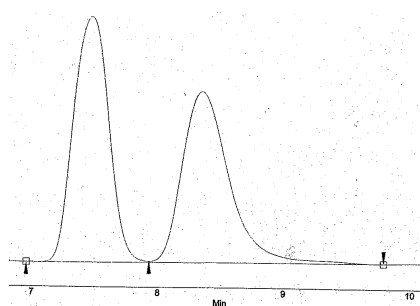
Start	Time	End	RT-Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[ $\mu$ V]	[ $\mu$ V.Min]	[%]
33.76	35.36	37.35	0.00	8.75	121.7	119.7	8.749
40.37	42.29	45.82	0.00	91.25	921.6	1248.7	91.251
				100.00	1043.3	1368.4	100.000



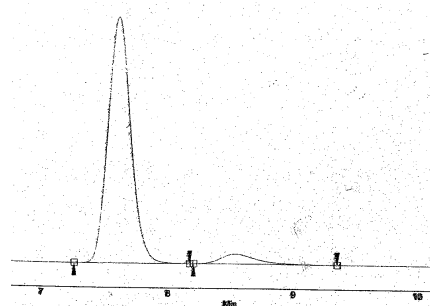
**(*S,5Z,7E*)-10-(*tert*-Butyldimethylsilyloxy)deca-1,5,7-trien-4-ol (1.40).**  $^1\text{H}$  NMR (400 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.05 (6H, s,  $\text{Si}(\text{CH}_3)_2$ ), 0.89 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.61 (1H, d,  $J = 4.2$  Hz, OH), 2.33 (4H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  and  $\text{CH}_2\text{CH}=\text{CH}$ ), 3.66 (2H, t,  $J = 6.6$  Hz,  $\text{SiOCH}_2$ ), 4.62 (1H, m, CHOH), 5.12-5.18 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.33 (1H, dd,  $J = 10.8, 8.8$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.71-5.87 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  and  $\text{CH}_2\text{CH}=\text{CH}$ ), 6.04 (1H, t,  $J = 11.2$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 6.38 (1H, ddt,  $J = 14.8, 11.2, 1.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  134.3, 133.8, 131.1, 130.7, 127.0, 118.5, 67.3, 62.9, 42.2, 36.6, 26.1, 18.6, -5.1 ppm; IR (neat): 3361.4 (br), 3077.2 (w), 2954.0 (s), 2929.6 (s), 2898.1 (m), 2857.5 (s), 1471.6 (m), 1255.6 (m), 1100.5 (s), 948.7 (m), 836.2 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{16}\text{H}_{29}\text{OSi}$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated 265.1988, found: 265.1986;  $[\alpha]_D^{20} = 2.34$  ( $c = 1.37$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel to afford a light yellow oil (82.1 mg, 83% yield) as a *E,Z* and *E,E* mixture (16:1).  $R_f = 0.51$  (3:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

**Proof of Stereochemistry:** Enantioselectivities were determined by comparison with authentic racemic material prepared through the use of tricyclohexylphosphine as the achiral ligand in the allylation reaction. The absolute stereochemistry was assigned by analogy.

*Chiral SFC (AD-H, Chiralpak, 220 nm, 1.0 mL/min, 2.0% MeOH, 150 psi, 50 °C) – analysis of (5Z,7E)-10-(tert-butyldimethylsilyloxy)deca-1,5,7-trien-4-ol.*



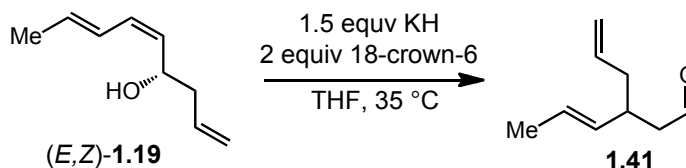
racemic



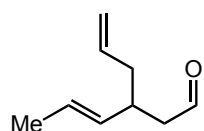
allylation product

Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	7.54	7.84	8.41	0.00	94.17	5158.7	1045.1	94.171
2	UNKNOWN	8.46	8.83	9.63	0.00	5.83	206.1	64.7	5.829
Total						100.00	5364.8	1109.8	100.000

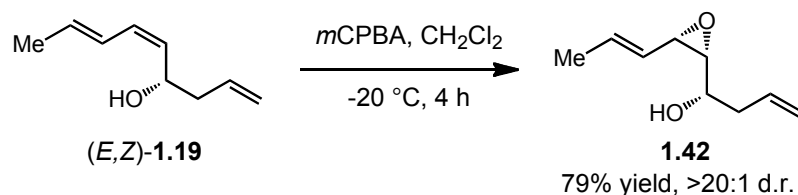
**7. Representative Procedures for the Functionalizations of (*S*,5*Z*,7*E*)-nona-1,5,7-trien-4-ol**



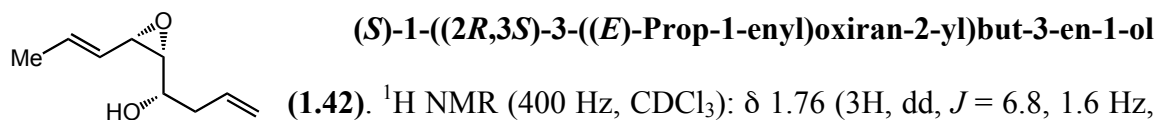
A flame-dried 10-mL round-bottom-flask equipped with a magnetic stir-bar was charged with 18.0 mg (0.45 mmol) of potassium hydride, 1.0 mL of THF and 158 mg (0.60 mmol) of 18-crown-6 in a drybox. The flask was sealed with septum, removed from the drybox and charged with 1.0 mL THF solution of (*E,Z*)-**1.19** (41.3 mg, 0.30 mmol) slowly under N<sub>2</sub>. The reaction mixture was heated to 35 °C and allowed to stir for 40 hours. The reaction was then cooled to ambient temperature and water was added to the reaction. The resulting mixture was diluted with diethyl ether and the organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated in *vacuo*. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine conversion of the starting material.



**(*E*)-3-Allylhex-4-enal (1.41).** The title compound was obtained only when (*E,E*)-**1.19** was utilized as substrate. The crude reaction mixture was purified on silica gel to afford a colorless oil (19.5 mg, 47% yield). *R<sub>f</sub>* = 0.73 (3:1 hexanes:EtOAc, stain in KMnO<sub>4</sub>). Spectral data are in accordance with literature references.<sup>13</sup>

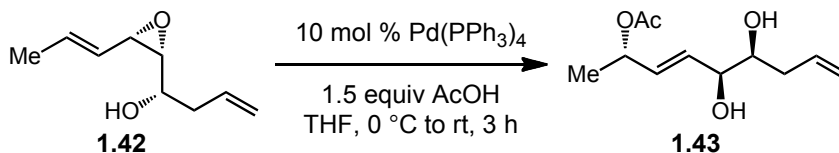


A flame-dried 25-mL round-bottom-flask equipped with a magnetic stir-bar was charged with 221 mg (1.60 mmol) of (*S*,5*Z*,7*E*)-nona-1,5,7-trien-4-ol, 8.01 mL of THF, and 336 mg (4.01 mmol) of NaHCO<sub>3</sub>. The flask was sealed with septum and cooled in a cryocool to -20 °C under N<sub>2</sub>. After 30 minutes, *m*CPBA (77%) was added as a white powder, and the mixture was allowed to stir at this temperature for another 4 hours. Then, the reaction was filtered through a plug of silica gel (prewashed with 5% triethylamine in ether), washed with ether, and concentrated under reduced pressure. The crude material was purified by silica gel (prewashed with 5% triethylamine in ether) chromatography (3:1 pentane:Et<sub>2</sub>O) to afford 195 mg (79% yield) of the title compound as light yellow oil and as a mixture of diastereomers (40:1 d.r.). *R*<sub>f</sub> = 0.59 (1:1 hexane/EtOAc, stain in KMnO<sub>4</sub>).

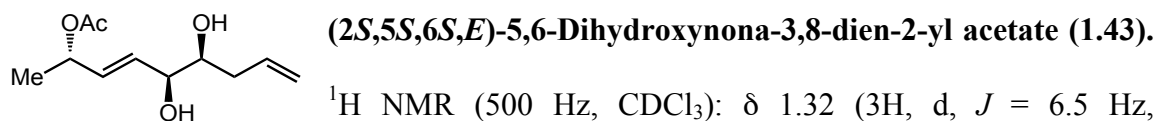


<sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>): δ 1.76 (3H, dd, *J* = 6.8, 1.6 Hz, CH<sub>3</sub>), 2.12 (1H, s, OH), 2.33 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.06 (1H, dd, *J* = 8.0, 4.4 Hz, CHOCHCHOH), 3.49 (1H, dd, *J* = 8.0, 4.4 Hz, CHOCHCHOH), 3.60 (1H, dtd, *J* = 7.6, 6.0, 4.0 Hz, CHOH), 5.12-5.18 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.33 (1H, ddd, *J* = 15.2, 8.0, 1.2 Hz, CH<sub>3</sub>CH=CH), 5.82 (1H, ddt, *J* = 17.2, 10.4, 6.8 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.97 (1H, dq, *J* = 15.2, 6.4 Hz, CH<sub>3</sub>CH=CH); <sup>13</sup>C NMR (100Hz, CDCl<sub>3</sub>): δ 133.9, 133.5, 124.9, 118.4, 69.4, 61.8, 58.0, 38.7, 18.3 ppm; IR (neat): 3415.0 (br),

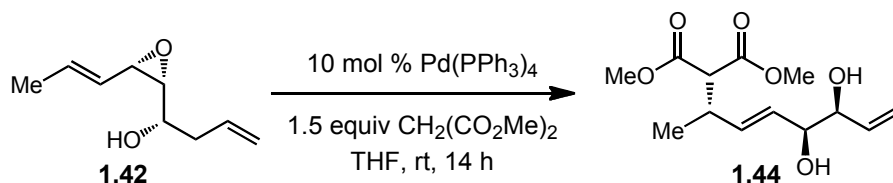
3077.0 (w), 3003.5 (m), 2970.6 (m), 2919.7 (m), 2857.1 (w), 1668.3 (w), 1641.9 (m), 1436.2 (m), 1378.2 (w), 1295.1 (br), 1047.3 (m), 963.5 (s), 914.4 (s), 873.4 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_9\text{H}_{13}\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]$ : calculated: 137.0966, found: 137.0973;  $[\alpha]_{\text{D}}^{20} = +1.5$  ( $c = 0.70$ ,  $\text{CHCl}_3$ ).



An oven-dried 2-dram vial was charged with 7.5 mg (0.0065 mmol) of tetrakis(triphenylphosphine)palladium, 0.20 mL of THF, and 5.8 mg (0.098 mmol) of acetic acid in a dry-box under an argon atmosphere. The vial was capped with a septum, taped with electrical tape, and removed from the dry-box. The reaction mixture was cooled in a ice-water bath for 30 minutes, and then 10.0 mg (0.0650 mmol) of (*S*)-1-((2*R*,3*S*)-3-((*E*)-prop-1-enyl)oxiran-2-yl)but-3-en-1-ol was added drop wise to the reaction vial as a solution in 0.14 mL of THF. The reaction was allowed to stir at 0 °C for 1 hour, followed by another 3 hours at ambient temperature. After this time period, the reaction was cooled to 0 °C again, followed by addition of about 10  $\mu\text{L}$  of  $\text{H}_2\text{O}_2$  (30% in water). Saturated  $\text{NaHCO}_3$  and ether were added and stirring continuously for 5 minutes, and the layers were separated. The aqueous layer was extracted with ether ( $\times 3$ ), and the organic layers were filtered through a plug of  $\text{MgSO}_4$  (top) and silica gel (bottom). Solvent was evaporated in *vacuo*. The crude material was purified by silica gel chromatography (1:1 pentane: $\text{Et}_2\text{O}$ ) to afford 8.1 mg (58% yield) of the title compound (10:1 1,4:1,2) as a colorless oil.  $R_f = 0.2$  (1:1 hexane/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ )

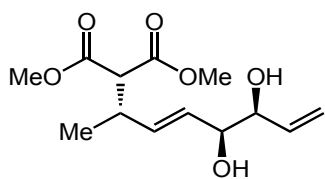


$^1\text{H}$  NMR (500 Hz,  $\text{CDCl}_3$ ):  $\delta$  1.32 (3H, d,  $J = 6.5$  Hz,  $\text{CH}_3\text{CHOAc}$ ), 2.05 (3H, s,  $\text{CH}_3\text{C(O)}$ ), 2.15-2.38 (4H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  and 2 OHs), 3.55 (1H, ddt,  $J = 8.0, 6.0, 4.0$  Hz,  $\text{CHOHCH}_2$ ), 3.98 (1H, m,  $\text{CH}=\text{CHCHOH}$ ), 5.13-5.17 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.36 (1H, p,  $J = 6.5$  Hz,  $\text{CH}_3\text{CHOAc}$ ), 5.77-5.89 (3H, m,  $\text{CH}=\text{CH}$  and  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  170.5, 134.3, 133.2, 130.9, 118.7, 74.9, 73.6, 70.4, 37.8, 21.6, 20.4 ppm; IR (neat): 3387.1 (br), 3114.3 (w), 2979.2 (w), 2930.9 (w), 2033.3 (w), 2005.8 (w), 1735.7 (s), 1641.5 (w), 1432.0 (w), 1372.4 (m), 1242.5 (s), 1043.2 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{11}\text{H}_{17}\text{O}_3$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated: 197.1178, found: 197.1181;  $[\alpha]_D^{20} = -31$  ( $c = 0.43$ ,  $\text{CHCl}_3$ ).



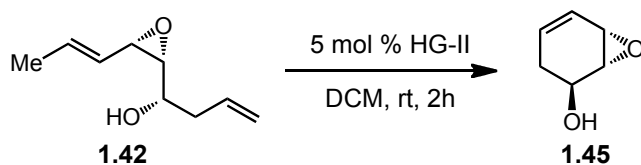
An oven-dried 2-dram vial was charged with 7.5 mg (0.0065 mmol) of tetrakis(triphenylphosphine)palladium, 0.20 mL of THF, and 12.9 mg (0.0975 mmol) of dimethylmalonate in a dry-box under an argon atmosphere. The vial was capped with septum, taped with electrical tape, and removed from the dry-box. Next, 10.0 mg (0.0650 mmol) of (*S*)-1-((2*R*,3*S*)-3-((*E*)-prop-1-enyl)oxiran-2-yl)but-3-en-1-ol was added to the reaction vial as a solution in THF (0.14 mL). The reaction was allowed to stir at ambient temperature for 14 hours. After this time period, the reaction was cooled to 0 °C,

followed by addition of about 10  $\mu\text{L}$  of  $\text{H}_2\text{O}_2$  (30% in water). Saturated  $\text{NaHCO}_3$  and ether were added and stirring continuously for 5 minutes, and the layers were separated. The aqueous layer was extracted with ether ( $\times 3$ ), and the organic layers were filtered through a plug of  $\text{MgSO}_4$  (top) and silica gel (bottom). Solvent was evaporated *in vacuo*. The crude material was purified by silica gel chromatography (3:1 hexane:EtOAc) to afford 16.0 mg (86% yield) of the title compound (17:1 d.r.) as a colorless oil.  $R_f = 0.2$  (1:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).

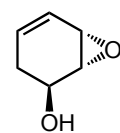


**Dimethyl 2-((2*S*,5*S*,6*S*,*E*)-5,6-dihydroxynona-3,8-dien-2-yl)malonate (1.44).**  $^1\text{H}$  NMR (500 Hz,  $\text{CDCl}_3$ ):  $\delta$  1.11 (3H,

d,  $J = 7.0$  Hz,  $\text{CHCH}_3$ ), 2.15 (1H, dddt,  $J = 14.5, 7.5, 8.0, 1.0$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.27-2.35 (3H, m,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$  and 2 OHs), 2.99 (1H, ddq,  $J = 8.5, 7.5, 7.0$  Hz,  $\text{CHCH}_3$ ), 3.33 (1H, d,  $J = 8.5$  Hz,  $\text{C(O)CHC(O)}$ ), 3.51 (1H, ddd,  $J = 8.0, 6.0, 4.0$  Hz,  $\text{CHOHCHOHCH}_2$ ), 3.70 (3H, s,  $(\text{OCH}_3)_a$ ), 3.73 (3H, s,  $(\text{OCH}_3)_b$ ), 3.92 (1H, dd,  $J = 6.5, 4.5$  Hz,  $\text{CHOHCHOHCH}_2$ ), 5.12-5.17 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.55 (1H, ddd,  $J = 15.5, 7.0, 1.0$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.72 (1H, ddd,  $J = 16.0, 8.5, 1.0$  Hz,  $\text{CH}=\text{CHCHOH}$ ), 5.84 (1H, dddd,  $J = 17.5, 10.5, 7.5, 6.5$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  168.78, 168.76, 135.2, 134.5, 130.8, 118.4, 75.2, 73.6, 57.6, 52.7, 52.6, 37.6, 37.0, 18.3 ppm; IR (neat): 3433.4 (br), 2955.5 (m), 1734.9 (s), 1641.3 (w), 1534.7 (m), 1243.5 (br), 1159.9 (m), 1062.7 (m), 1018.7 (m), 976.3 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{21}\text{O}_5$  [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ]: calculated: 269.1389, found: 269.1382;  $[\alpha]_D^{20} = -20$  ( $c = 0.88$ ,  $\text{CHCl}_3$ ).



A flame-dried round-bottom-flask was charged with 2.0 mg (0.0032 mmol) of Hoveyda-Grubbs II catalyst, 6.0 mL of  $\text{CH}_2\text{Cl}_2$ , and 10.0 mg (0.0650 mmol) of (*S*)-1-((2*R*,3*S*)-3-((*E*)-prop-1-enyl)oxiran-2-yl)but-3-en-1-ol in  $\text{CH}_2\text{Cl}_2$  (0.5 mL). The reaction was allowed to stir at ambient temperature under  $\text{N}_2$  for 2 hours. After this time period, solvent was evaporated *in vacuo*, and the crude material was purified by silica gel chromatography (2:1 pentane:ether) to afford 5.9 mg (81% yield) of the title compound (17:1 d.r.) as a colorless oil.  $R_f = 0.23$  (1:1 hexane:EtOAc, stain in  $\text{KMnO}_4$ ).


**(1*R*,2*S*,6*S*)-7-Oxabicyclo[4.1.0]hept-4-en-2-ol.**  $^1\text{H}$  NMR (500 Hz,  $\text{CDCl}_3$ ):  $\delta$  1.53 (1H, d,  $J = 8.5$  Hz, OH), 2.27 (1H, ddt,  $J = 17.5, 6.5, 2.0$  Hz,  $\text{CH}_a\text{H}_b$ ), 2.37 (1H, dddd,  $J = 17.0, 6.0, 3.5, 3.0$  Hz,  $\text{CH}_a\text{H}_b$ ), 3.34 (1H, td,  $J = 4.0, 1.5$  Hz,  $\text{CHOHCHOCH}$ ), 3.51 (1H, ddd,  $J = 4.0, 2.5, 2.0$  Hz,  $\text{CHOH}$ ), 4.43 (1H, m,  $\text{CHOHCHOCH}$ ), 5.82 (1H, ddm,  $J = 9.5, 6.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}$ ), 6.06 (1H, dt,  $\text{CH}_2\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  129.6, 124.1, 64.1, 55.9, 47.0, 30.6 ppm; IR (neat): 3412.5 (br), 3041.1 (w), 2993.0 (w), 2923.0 (s), 2852.8 (m), 1641.8 (w), 1418.5 (m), 1398.1 (m), 1050.9 (s), 1036.0 (s), 981.1 (s), 952.2 (m), 885.9 (s), 805.2 (s), 771.3 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_6\text{H}_9\text{O}_2$  [ $\text{M}+\text{H}$ ]: calculated: 113.0603, found: 113.0597;  $[\alpha]_D^{20} = -79$  ( $c = 0.42$ ,  $\text{CHCl}_3$ ).



## Chapter II

### The Metal-Catalyzed Cross-Couplings Involving Allyl Metal Reagents

#### I. INTRODUCTION

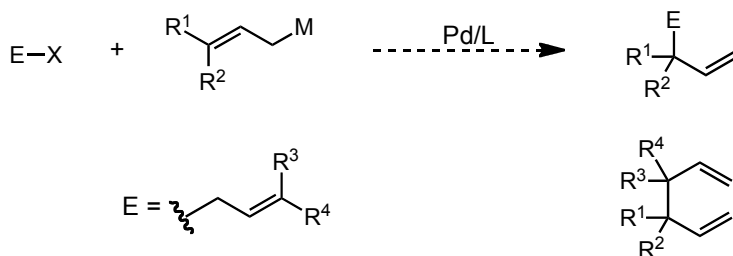
The metal-catalyzed cross-coupling of organic electrophiles and organometal reagents, especially reactions accomplished with palladium-catalysis, has been extensively developed and has played significant role in the construction of carbon-carbon and carbon-heteroatom bonds in the synthesis of complex molecules.<sup>1</sup> Strikingly, despite the pioneering investigation of Pd-catalyzed allylation with allyltins,<sup>2</sup> subsequent studies have been almost totally dominated by allylations with allylic electrophiles. The reason for the general difficulties associated with the use of allylmetals in Pd-catalyzed allylation is still unclear, but could be due to stability issues or their ability to poison Pd(II) intermediates. The lack of regioselectivity greatly restricts their application in the synthesis of complex molecules. In allyl-allyl cross-coupling, in particular, the use of an allylmetal is unavoidable, and accordingly this reaction is severely underdeveloped. From a synthetic standpoint, the cross-coupling of allyl electrophiles and allylmetal reagents is very attractive because it has the capacity to establish two new stereogenic centers during the formation of an  $sp^3$ - $sp^3$  carbon-carbon bond (Scheme 2.1).

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<sup>1</sup> *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

<sup>2</sup> Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

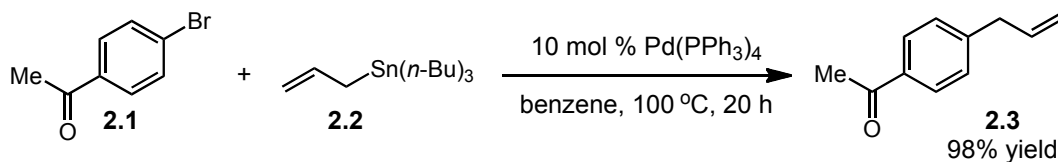
**Scheme 2.1**



## II. METAL-CATALYZED ARYL-, ACYL- AND ALKENYL-ALLYL COUPLINGS

**A. Allyltin Reagents in Palladium-Catalyzed Couplings.** Allylstannanes are among the most studied allylmetal building blocks for Pd-catalyzed aryl-, acyl- and alkenyl-allyl coupling. They are, however, underutilized stannane reagents in Stille coupling presumably because of difficulties with the synthesis of regiochemically defined allyltin reagents, and their tendency for allylic isomerization. Initial investigation of simple allylic stannanes in the cross-coupling with aryl halides has exhibited smooth reactions under mild conditions with  $Pd(PPh_3)_4$  as the catalyst,<sup>1</sup> though they gave lower reactivity than alkenylstannanes (Scheme 2.2).<sup>3</sup>

**Scheme 2.2**

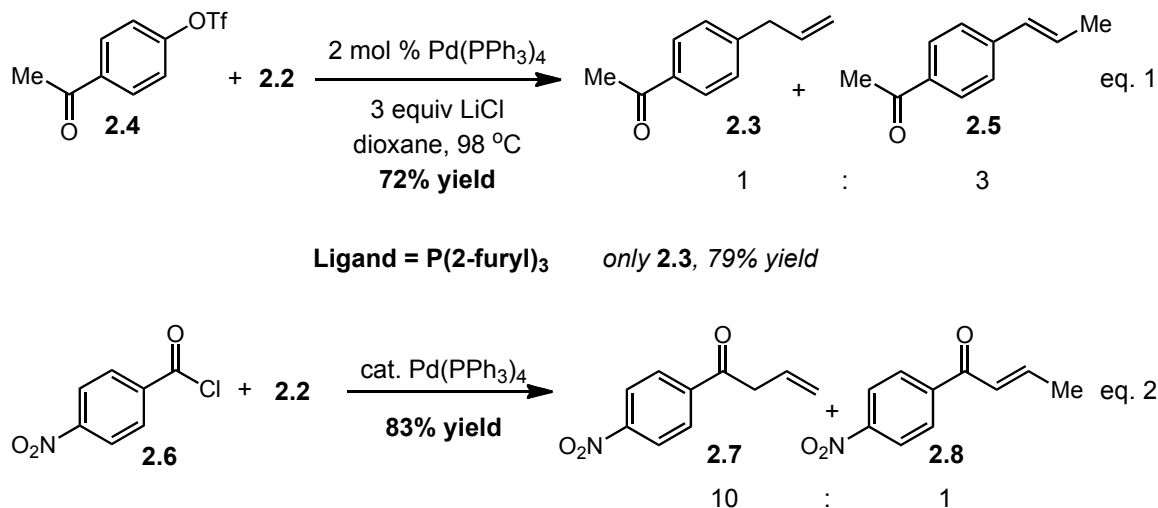


One common problem associated with Pd-catalyzed cross-coupling between organoelectrophiles and allyltins was observed when aryl triflates and acyl chlorides were

<sup>3</sup> Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1985**, 25, 508.

used as substrates. As shown in Scheme 2.3, the alkenes in the product tend to isomerize into conjugation with the aromatic<sup>4</sup> group or carbonyl<sup>5</sup> after coupling. This sometimes can be prevented by the choice of suitable ligands, with a concomitant acceleration of the reaction rate.<sup>6</sup>

**Scheme 2.3**



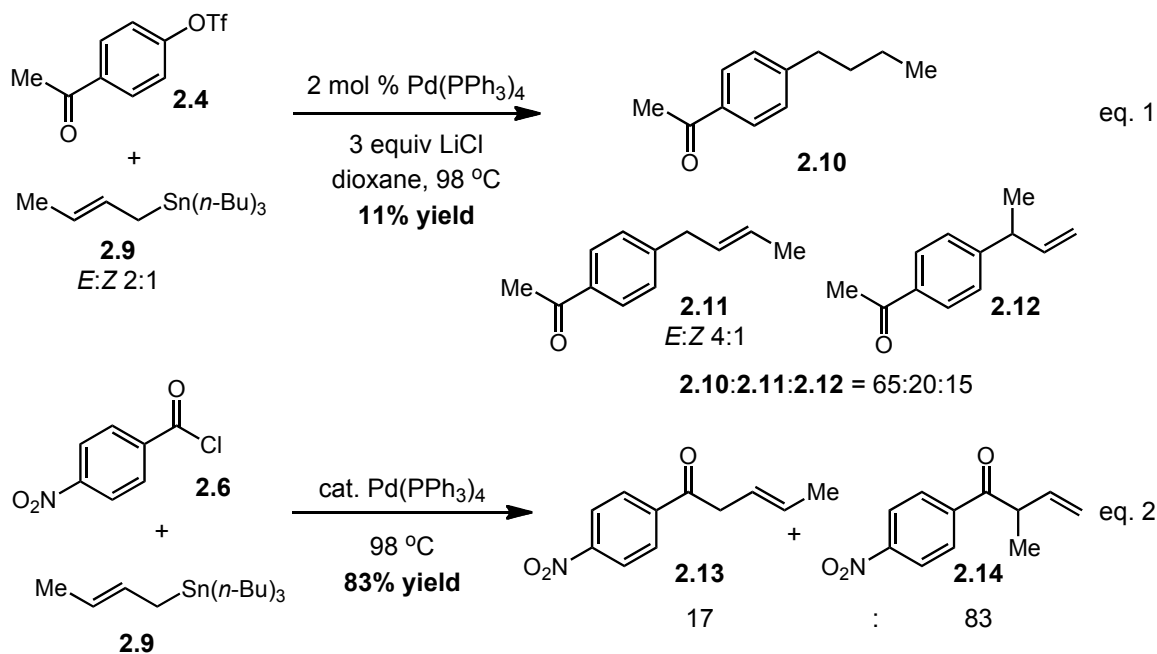
Efforts to explore more substituted allyltin reagents, such as crotylstannane, has revealed difficulties in controlling both chemoselectivity and regioselectivity (Scheme 2.4). Poor chemoselectivity results in the formation of significant amounts of aryl-butyl coupling product (**2.10**) in competition with the allylation products **2.11** or **2.12**. Both  $\alpha$ - and  $\gamma$ -substitution products are generated due to the lack of regiocontrol in both aryl-<sup>4</sup> and acyl-couplings.<sup>5</sup>

<sup>4</sup> Echavarren, A. W.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

<sup>5</sup> Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.

<sup>6</sup> Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

### Scheme 2.4



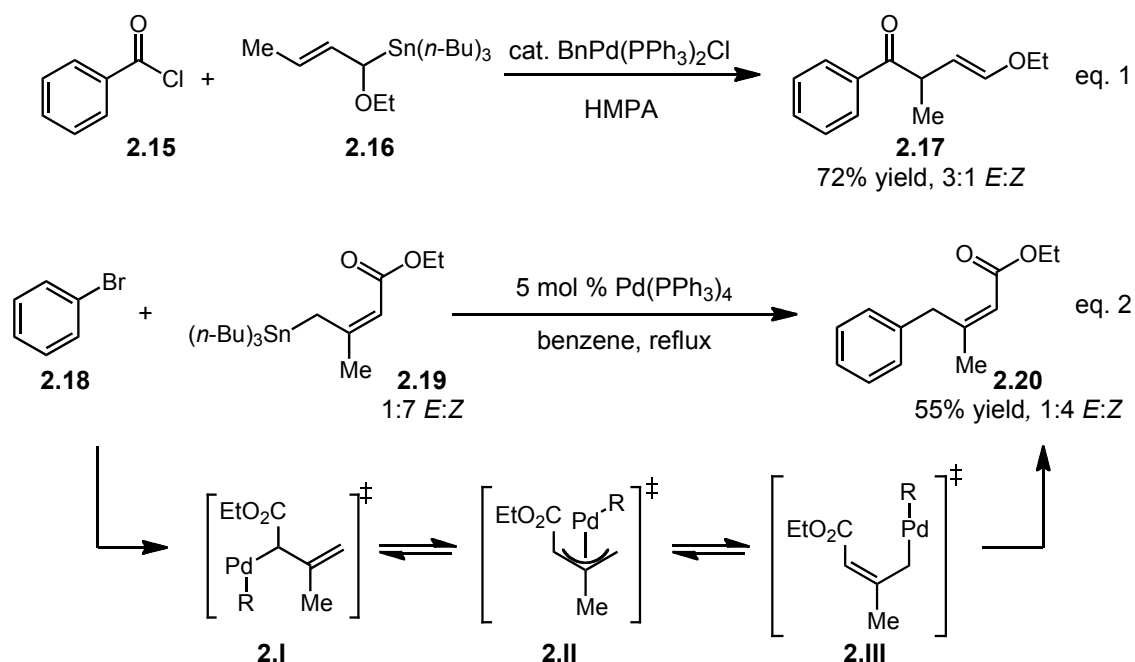
Regiocontrol has been observed with a few classes of substituted allylstannanes, however, not enough data are present in the literature to draw firm conclusions on the origin of  $\alpha$ - and  $\gamma$ -selectivity. An interesting example is shown in equation 1 (Scheme 2.5) where  $\alpha$ -alkoxylallyltins couple with acyl chlorides to afford the  $\gamma$ -oxygenated  $\beta,\gamma$ -unsaturated ketones, which can be further converted to 1,4-dicarbonyl compounds by acid hydrolysis.<sup>7</sup>

As another example, a carbon-carbon bond forms selectively at the  $\gamma$ -position of the tin dienolates (equation 2), delivering  $\gamma$ -substituted dienolate products under Pd-catalysis. These types of compounds are of great synthetic importance because the  $\alpha$ -substituted products are normally favored under non-catalyzed conditions with other

<sup>7</sup> Verlhac, J.; Pereyre, M. *Tetrahedron* **1990**, 46, 6399.

organometal reagents such as organolithiums.<sup>8</sup> It is proposed by the authors that transmetallation of allyltin onto the initially formed Pd(II) complex (obtaining by oxidative addition) leads to Pd-allyl complex, which undergoes reductive elimination at the less sterically hindered site and affords the observed product. Although not studied experimentally, this proposal explains the selectivity towards less hindered  $\gamma$ -position as well as the *E:Z* ratio change between substrate (e.g. **2.19**) and product (e.g. **2.20**):  $\sigma$ - $\pi$ - $\sigma$  isomerization (**2.I-2.II-2.III**) could happen in the Pd-allyl complex before carbon-carbon bond formation, contributing to the observed change in *E:Z* ratio.

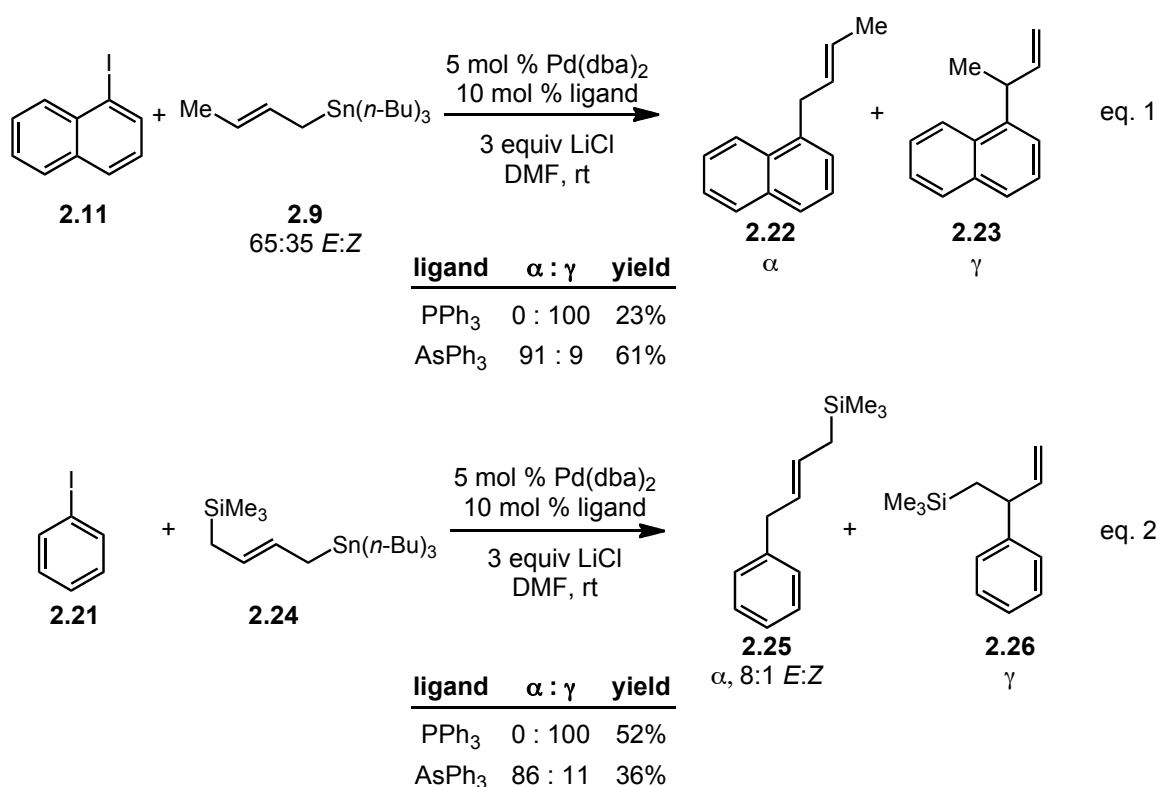
**Scheme 2.5**



<sup>8</sup> (a) Yamamoto, Y.; Hatsuya, S.; Yamada, J. *J. Chem. Soc., Chem. Comm.* **1988**, 86. (b) Yamamoto, Y.; Hatsuya, S.; Yamada, J. *J. Org. Chem.* **1990**, 3118.

Regioselectivity can be enhanced by suitable choice of ligands for the coupling reaction. As shown in scheme 2.6, changing the ligand allows for both  $\alpha$ - and  $\gamma$ -coupling products to be synthesized from the same allyltin reagents, substrates and palladium precursor.<sup>9</sup>  $\text{PPh}_3$  favors the  $\gamma$ -product, whereas softer and more dissociating  $\text{AsPh}_3$  affords the  $\alpha$ -isomer preferably.  $\text{LiCl}$  is critical for high conversion, presumably because ligand exchange with chloride ion in the catalytic cycle facilitates the coupling reaction.<sup>10</sup> It is also worth noting that these reactions suffer from low  $E:Z$  selectivity and low yield, which arises from low conversion.

**Scheme 2.6**



<sup>9</sup> Obora, Y.; Tsuji, Y.; Kobayashi, M.; Kawamura, T. *J. Org. Chem.* **1995**, 60, 4647.

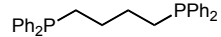
<sup>10</sup> Scott, W. J.; McMurry, J. E. *ACC. Chem. Res.* **1988**, 21, 47.

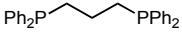
**B. Allylsilanes.** In contrast to allylstannanes, substituted allylsilanes exhibit high regiocontrol during the Pd-catalyzed coupling with organic halides and triflates. As shown in equation 1 (Scheme 2.7),  $\gamma$ -substituted products are formed exclusively in regiochemically pure form with careful choice of fluoride source and ligands.<sup>11</sup> Further investigation into this reaction has also allowed for the  $\alpha$ -selective allylation, where an appropriate phosphine ligand is necessary for high regioselectivity (equation 2).<sup>12</sup> A mechanism has been proposed by the authors to explain the origins of the observed ligand-dependent-regioselectivity. The catalytic cycle begins with the oxidative addition of Ar-X to a palladium(0), followed by transmetallation with activated allyltetrafluorosilicate in an S<sub>E</sub>2' fashion (electrophilic attack of arylPd(II) complex on the double bond of allylsilicate exclusively takes place on the  $\gamma$ -carbon) to yield allyl(aryl)palladium complexes **2.V**.<sup>13</sup> Rapid reductive elimination of **2.V** should give  $\gamma$ -coupled products. Diphosphine ligands such as dppb<sup>14a</sup> and monodentate ligands like PPh<sub>3</sub>, which render wide P-M-P angles, are considered to sterically accelerate the reductive elimination, thereby favoring predominant formation of the  $\gamma$ -product.<sup>15</sup> In contrast less sterically hindered ligands like dppp<sup>14b</sup> or dppe<sup>14c</sup> (equation 2), slower reductive elimination occurs and allows for the isomerization of the  $\eta^1$ -allylPd complex **2.V** to more stable **2.VI** before carbon-carbon bond formation.

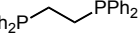
<sup>11</sup> Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

<sup>12</sup> Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511.

<sup>13</sup> Hatanaka, V.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279.

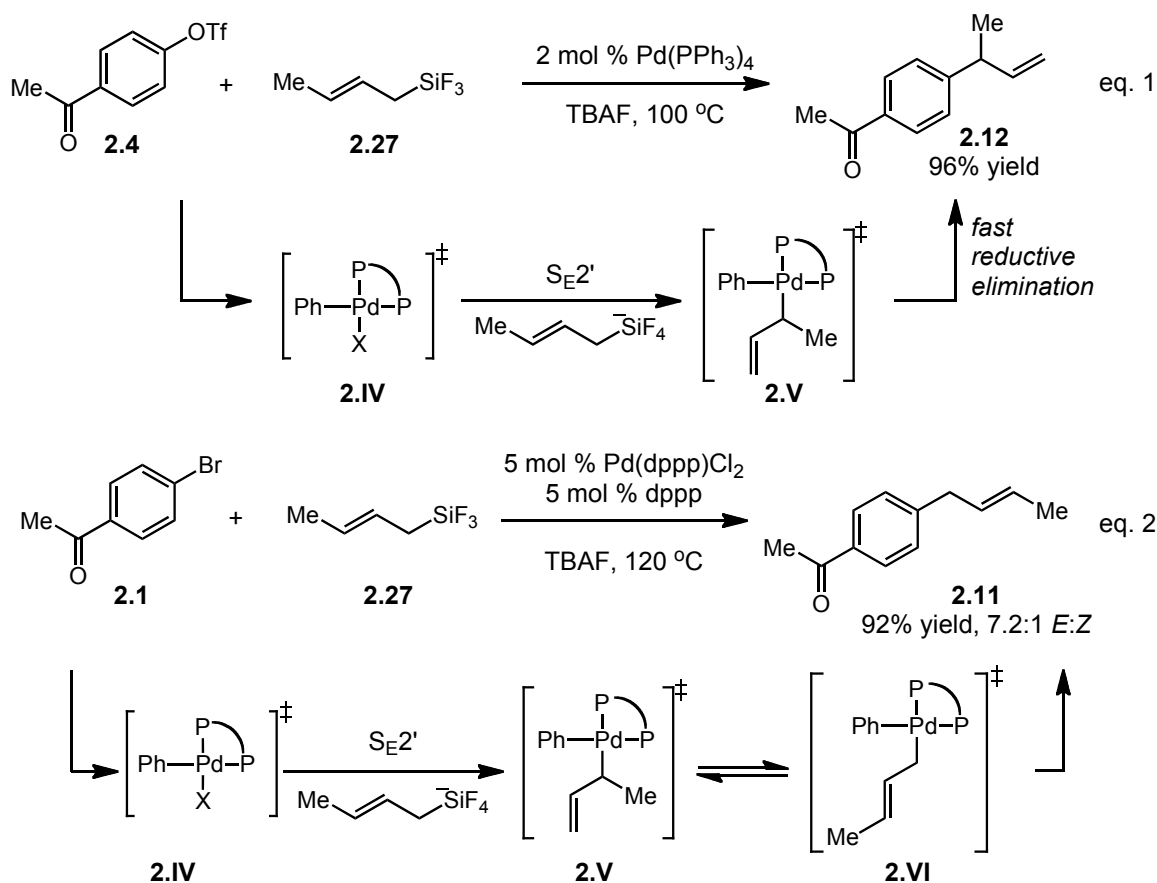
<sup>14</sup> (a) Structure of diphenylphosphinobutane (dppb): 

(b) Structure of diphenylphosphinopropane (dppp): 

(c) Structure of diphenylphosphinoethane (dppe): 

<sup>15</sup> Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.

**Scheme 2.7**



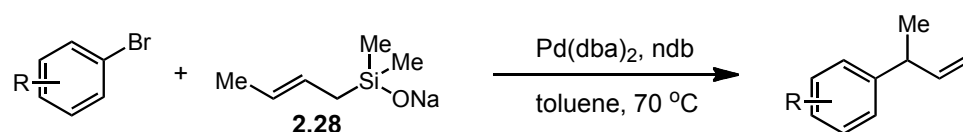
The  $S_E2'$  transmetalation of Pd(II) complexes with allyltetrafluorosilicates has also been applied in the cross-coupling between optically active allylsilanes and organoelectrophiles. High chirality transfer can be achieved with the appropriate choice of fluoride sources and solvent. Due to competing *syn* and *anti* transmetalation products with opposite absolute configurations can be obtained.<sup>13</sup>

Further studies on substituted allylsilane reagents in the Pd-catalyzed cross-couplings have also revealed allylic silanolate salts as versatile building blocks that do not require external activation. As shown in Scheme 2.8, aromatic bromides undergo



smooth coupling with sodium allyldimethylsilanolate under mild neutral conditions, delivering only  $\gamma$ -substituted allylation products.<sup>16</sup> The oxygen anion on the silanolate is believed to be responsible for the high reactivity of these reagents, promoting  $S_E2'$  transmetallation by coordinating to Pd(II), and assuring  $\gamma$ -selectivity. Such unique Si-O-Pd linkage, through which intramolecular delivery of arylpalladium electrophiles takes place, enables almost complete chirality transfer when optically pure allylic silanolates are used as nucleophiles.<sup>17</sup>

**Scheme 2.8**



**C. Allylborons.** Allylboron reagents are attractive to synthetic organic chemists due to their low toxicity, readily availability, and higher stability compared to many other allylmetal building blocks. More recently, they have been employed in the palladium-catalyzed cross-coupling reactions with organic electrophiles. Pioneered by Yamamoto and Miyaura,<sup>18</sup> potassium allyltrifluoroborates react with aryl and alkenyl halides to deliver  $\gamma$ -substituted coupling products with greater than 99:1 regioselectivity. Such high levels of regiocontrol are believed to be a result of the ligand. Optimal ligands, such as D-*t*-BPF (**2.30**, Scheme 2.9) give only  $\gamma$ -coupling across twenty substrates. The same group has also identified a chiral bidentate ligand that promotes allyl-aryl (or alkenyl) coupling

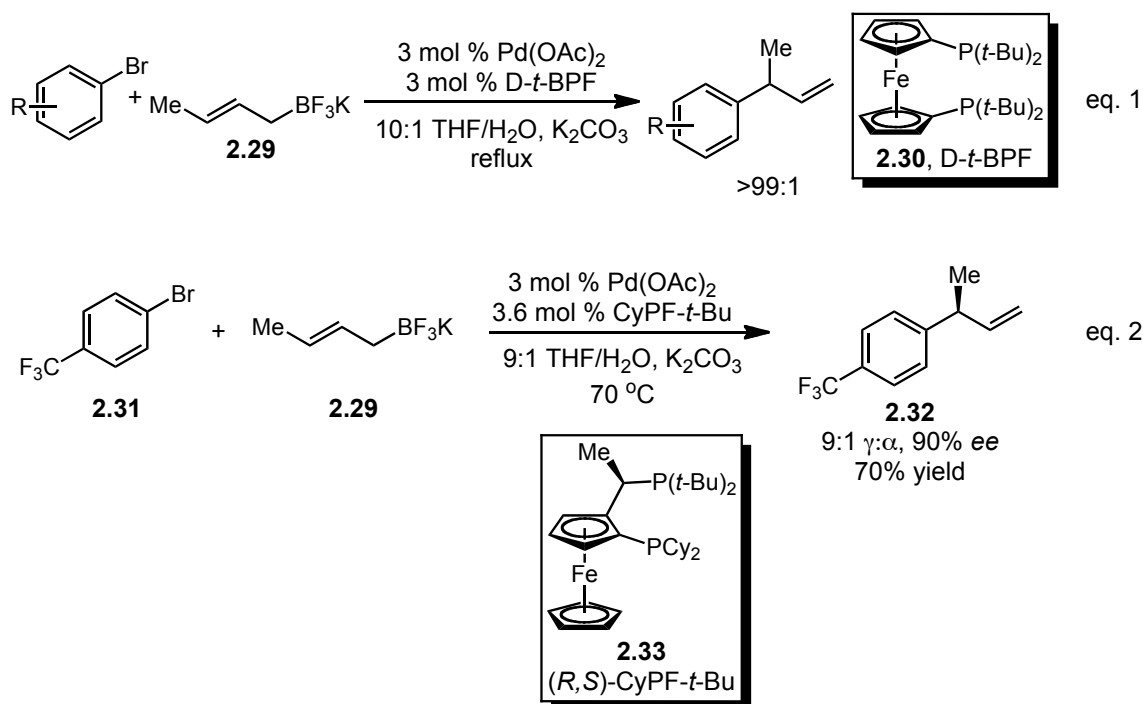
<sup>16</sup> Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382.

<sup>17</sup> Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2010**, *132*, 3612.

<sup>18</sup> Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704.

in an enantioselective fashion, presenting the first asymmetric method for Pd-catalyzed cross-coupling between allylmetals and organoelectrophiles.<sup>19</sup> As shown in equation 2, Scheme 2.9, branch-allylated compounds can be synthesized in up to 90% *ee*. The use of 9:1 mixture of THF and H<sub>2</sub>O is critical for both high regioselectivity and enantioselectivity.

**Scheme 2.9**



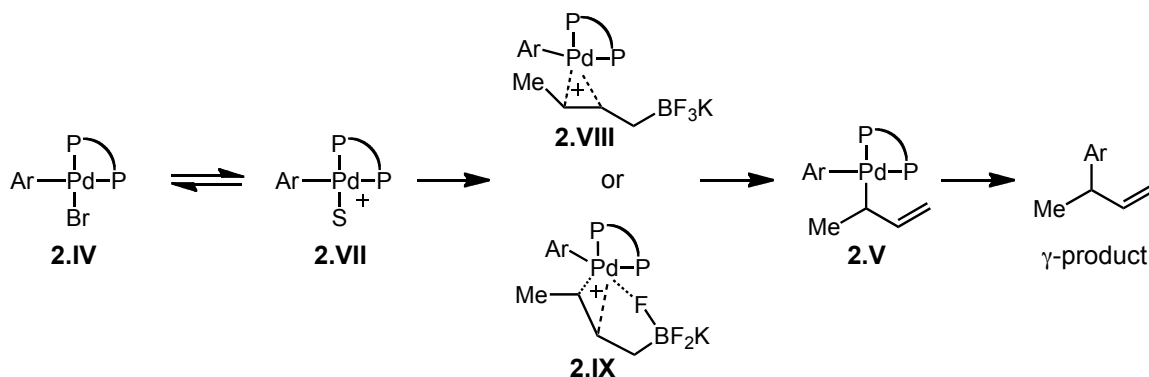
One of the unique aspects in the mechanism, the formation of an unprecedented highly electrophilic  $[\text{Pd}(\text{Ar})(\text{D-t-BPF})]^+$  (**2.VII**, Scheme 2.10) before transmetallation with allyltrifluoroborates, has been supported by kinetic studies.<sup>20</sup> Kinetic data in the coupling of *para*-substituted bromoarenes with **2.29** shows a linear positive correlation

<sup>19</sup> Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, 35, 1368.

<sup>20</sup> Yamamoto, Y.; Takada, S.; Miyaura, N. *Organometallics* **2009**, 28, 152.

acceleration by donating substituents. Theoretical study by DFT calculation suggests the transmetallation between the cationic oxidative addition adduct **2.VII** with trifluoroborates proceeds via an open  $S_E2'$  (**2.VIII**) transition state, which is favored over the closed one (**2.IX**). The origins of the enantioselectivity when applying CyPF-*t*-Bu as the chiral ligand are still under investigation.

**Scheme 2.10**



Though they have been utilized in the Pd-catalyzed cross-coupling between substituted allylborons with organoelectrophiles, monodentate ligands such as  $\text{PPh}_3$  deliver both  $\alpha$ -<sup>21</sup> and  $\gamma$ -substituted<sup>22</sup> products in an unpredictable fashion. Therefore, they are much less studied in this type of transformation.

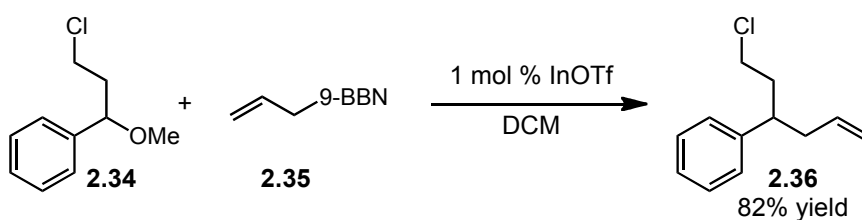
**D. Aryl-, Acyl-, Alkenyl- and Alkyl-Allyl Cross-Couplings Catalyzed by Metals Other Than Pd.** Transition metals other than Pd, as well as main group metals, can also catalyze cross-coupling between allylmetals and organoelectrophiles. Indium(I)

<sup>21</sup> Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, 3964.

<sup>22</sup> Dai, Q.; Xie, X.; Xu, S.; Ma, D.; Tang, S.; She, X. *Org. Lett.* **2011**, 13, 2302.

triflate catalyzes the smooth alkyl-allyl coupling reaction between benzyl ethers and allylboranes, delivering benzylic allylation products in moderate yields (Scheme 2.11).<sup>23</sup> The indium(I) catalyst is proposed by the authors to play a dual role in the catalytic cycle: acting as a Lewis acid to facilitate the carbon-oxygen bond cleavage, and the resulting indium methoxide triggers transmetallation. Combination of an indium allyl with a carbenium results in the new carbon-carbon bond formation.

**Scheme 2.11**



More recently, Cu(II) (Scheme 2.12),<sup>24</sup> Ag(I)<sup>25</sup> and Co(II)<sup>26</sup> have been reported to catalyze the allylation of alkyl halides or pseudohalides with allylic Grignard reagents, likely through radical mechanisms. Intramolecular couplings have also been explored within these methods, with the most success forming five-member ring adducts.  $\gamma$ -Substituted allylic Grignard building blocks deliver both  $\alpha$ - and  $\gamma$ -coupled products; the regioselectivity is greatly dependent upon the substrates and reaction conditions. Unfortunately, the lack of regiocontrol limits their further application.

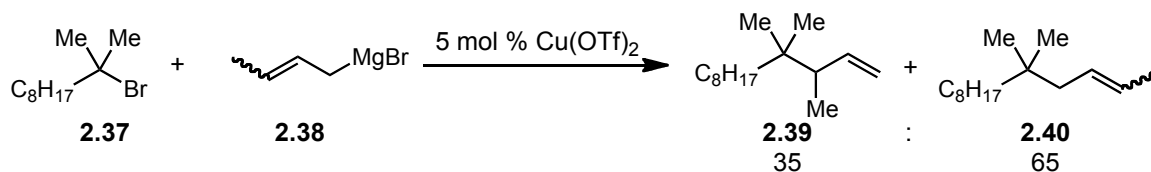
<sup>23</sup> Dao, H.; Schneider, U.; Kobayashi, S. *Chem. Comm.* **2011**, 47, 692.

<sup>24</sup> Sai, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, 82, 1194.

<sup>25</sup> Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, 10, 969.

<sup>26</sup> (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, 4137. (b) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, 5640.

### Scheme 2.12



As another interesting example, Rh(I) is able to catalyze the allylations of benzyl acetates with allylsilanes in good yields and great regiocontrol, delivering only  $\gamma$ -allylated products when substituted allylsilanes are utilized as substrates.<sup>27</sup> Chiral ligands have also been employed in an attempt to synthesize optically active coupling products, however, starting materials remained untouched after the reaction.

## III. METAL-CATALYZED ALLYL-ALLYL CROSS-COUPLING

**A. Pd-Catalyzed Allyl-Allyl Coupling.** Independent work from Stille<sup>28</sup> and Trost<sup>29</sup> initially revealed that Pd complexes such as  $\text{BnClPd}(\text{PPh}_3)_2$  and  $\text{Pd}(\text{PPh}_3)_4$  are able to catalyze the coupling between allylic bromides and acetates with allylstannanes to afford 1,5-dienes as coupling products (Scheme 2.13). Although they are both suitable substrates for this reaction, the allylic acetates are always converted to the branched products regardless of the reaction conditions when  $\gamma$ -substituted allyltins utilized as nucleophiles in the transformation. The bromide analogues, however, deliver mixtures of branched and linear products in an unpredictable fashion. Similar phenomena have also

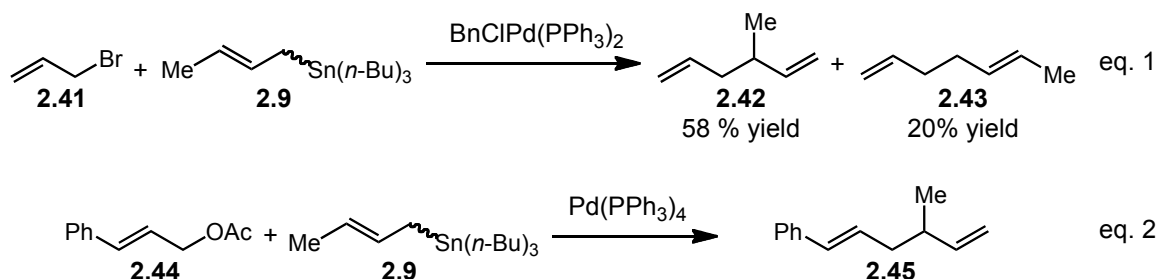
<sup>27</sup> Onodera, G.; Yamamoto, E.; Tonegawa, S.; Iezumi, M.; Takeuchi, R. *Adv. Synth. Catal.* **2011**, 353, 2013.

<sup>28</sup> Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, 21, 2599.

<sup>29</sup> Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 21, 2595.

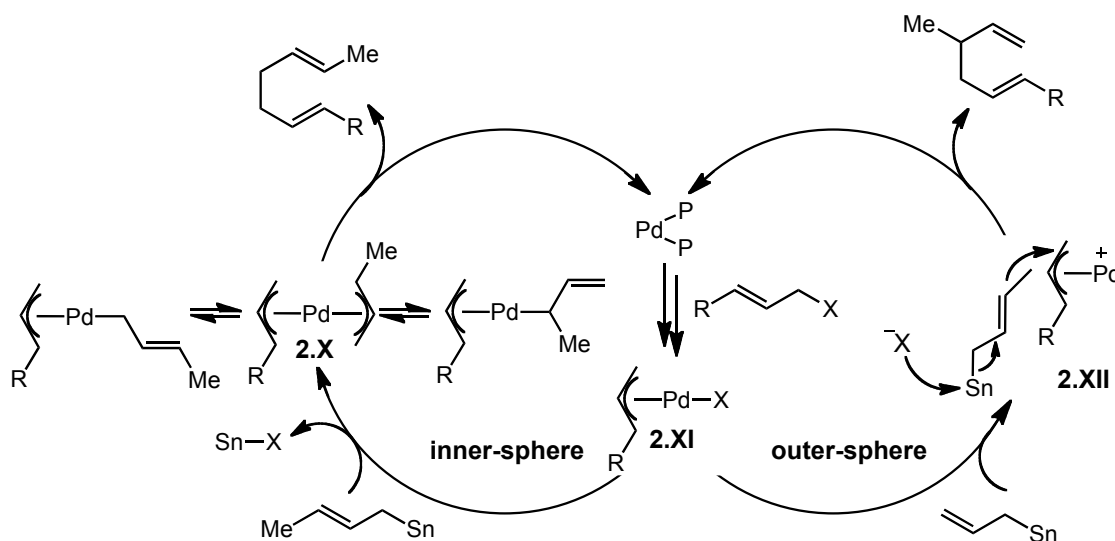
been observed in later studies on the Pd-catalyzed allyl-allyl cross-coupling with both allylstannanes<sup>8b</sup> and allylsilanes<sup>11</sup> as nucleophiles.

**Scheme 2.13**



The origins of the difference between the two substrate classes are of great interest, and taking advantage of this distinct reactivity could lead to more useful methodologies. Since oxidative addition of allylic electrophiles to Pd(0), and transmetallation of allyltin reagents onto the resulting Pd(II) complexes are both known, an inner-sphere mechanism was proposed which would afford a new carbon-carbon bond after reductive elimination of **2.X** (Scheme 2.14). Based on this proposal the regioselectivity should depend on substrates, ligands and reaction conditions, the parameter that presumably affect the rate of reductive elimination and isomerization of bis(allyl)Pd(II) complexes. The observations with allylic bromide substrates match the proposed inner-sphere mechanism, but the regioselectivity associated with allylic acetates is not consistent with this proposal: in this case an outer-sphere mechanism seems more reasonable: as shown in Scheme 2.14, a Pd- $\pi$ -allyl complex forms upon oxidative addition, which is then attacked by allylstannane nucleophiles to form the carbon-carbon bond at the  $\gamma$ -carbon (**2.XII**).

**Scheme 2.14**

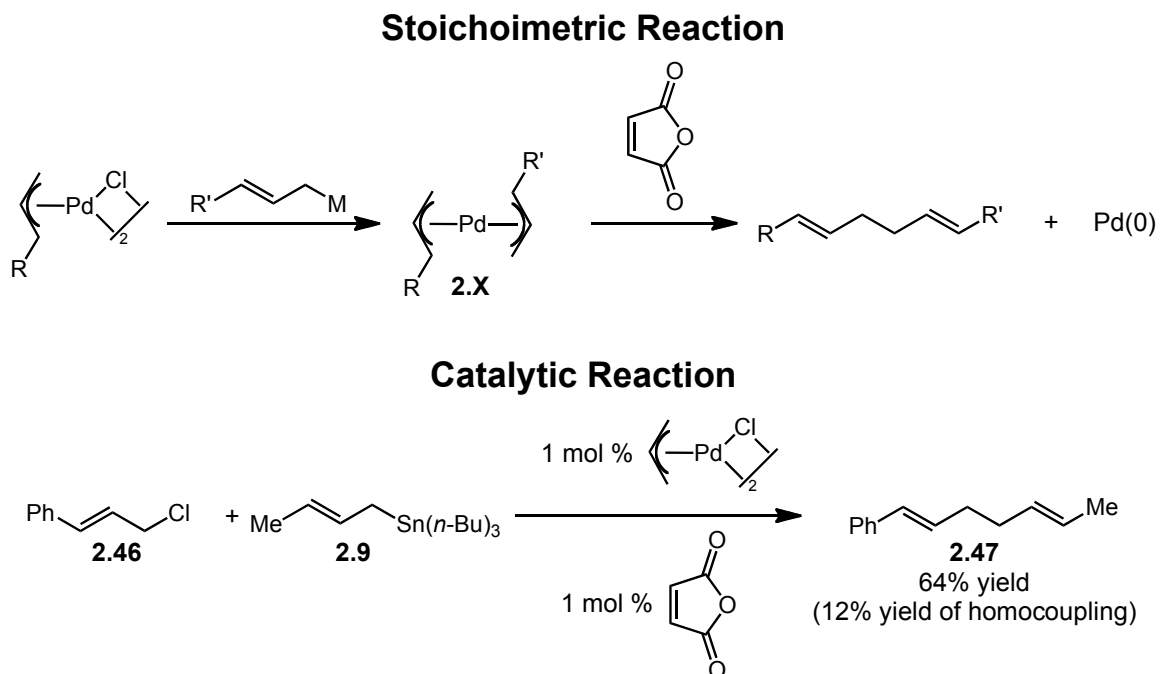


In an inspiring study, the Schwartz group achieved allyl-allyl cross-coupling with Pd-catalysis. Starting with Pd- $\pi$ -allyl complexes, transmetalation with another allylmetal specie, either allyllithiums or allylic Grignards, delivers bis( $\pi$ -allyl)palladium(II) complexes (**2.X**, Scheme 2.15) as stable intermediates.<sup>30</sup> The allylic coupling is then accomplished with activation by a  $\pi$ -acidic ligand, such as maleic anhydride, to generate corresponding 1,5-dienes as well as a Pd(0) species. Head-to-head coupling is generally preferred in this transformation, wherein linear products are formed selectively, although the regioselectivity can be low depending on the substrates. Further study suggests the importance of  $\pi$ -acidic ligands, without which either no coupling occurs or undesired hydride transfer products form. Catalysis of the reaction between allylic halides and allylstannanes is thought to proceed through Pd-catalysis. Maleic anhydride is critical to

<sup>30</sup> (a) Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028. (b) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779.

enable the formation of the desired carbon-carbon bond. Compared to the stoichiometric reactions, the catalytic transformation predominately yield linear products. The reaction efficiency, however, is generally low due to the formation of significant amount of homocoupling products.

**Scheme 2.15**

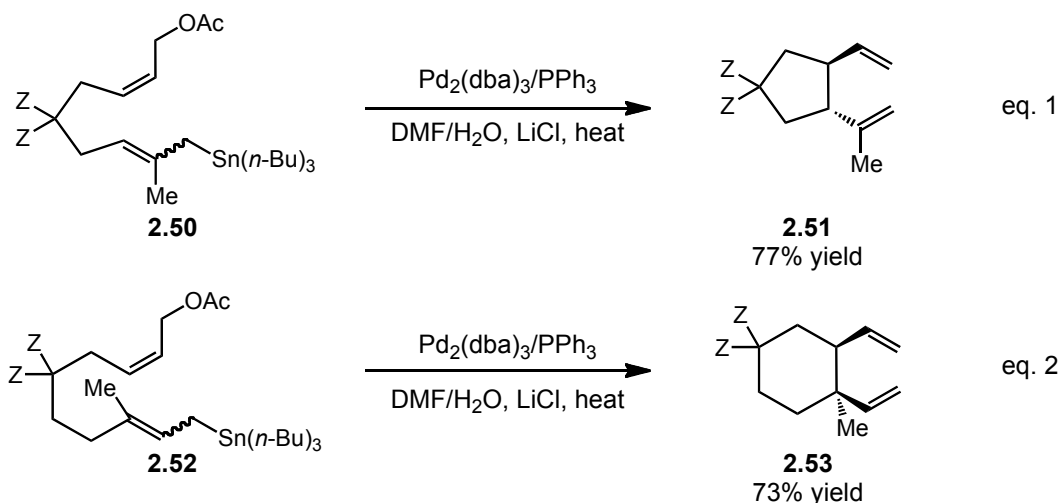


In the following chapter, a highly regio- and enantioselective Pd-catalyzed allyl-allyl cross-coupling will be described. In this reaction, relatively non-toxic and commercially available allylB(pin) (**2.49**, Scheme 2.16) is employed as the allylmatal reagent. Prior to describing our results, aligned studies in catalysis will be described. Shortly after our identification of the effective means for the regiocontrol in allyl-allyl couplings, a Pd- and Ni-catalyzed allylic coupling between allyl carbonates and allylB(pin)





**Scheme 2.17**



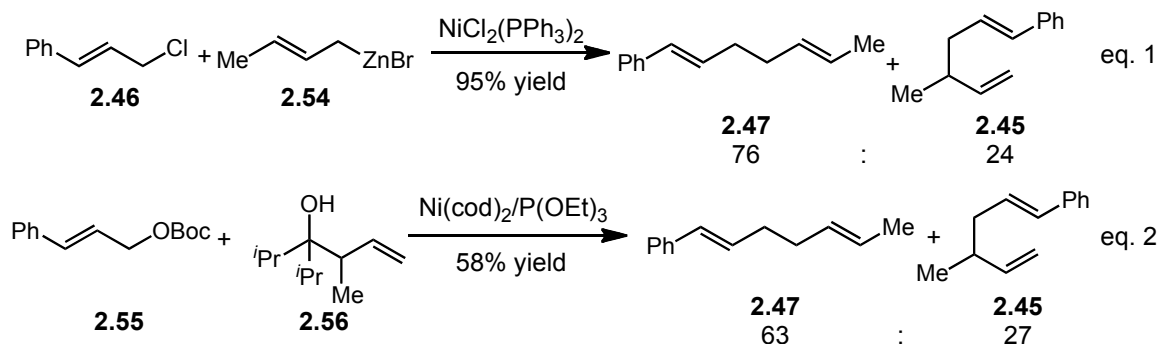
**B. Allyl-Allyl Cross-Coupling Catalyzed by Metals Other Than Pd.** Nickel shares a number of similarities with palladium in chemical reactivity, especially in organometallic catalysis. Due to its low cost and high natural abundance, it is of great interest to examine Ni in reactions in which palladium is an active promoter. Based on preliminary investigations, Ni can effectively catalyze the coupling of allylic halides and allylic zinc reagents, affording both head-to-head and head-to-tail products (Scheme 2.18).<sup>34</sup> In a related process, tertiary homoallylic alcohols were reported recently to serve as allylic nucleophiles in the Ni-catalyzed allylic coupling reaction, starting with readily available allylic carbonates as electrophiles (equation 2).<sup>35</sup> Subsequent to  $\pi$ -allyl formation by reaction between  $\text{Ni}(0)$  and the allylic carbonates, Ni-mediated retro-allylation delivers the second allyl ligand to  $\text{Ni}(\text{II})$ . *In situ* activation by the alkoxides generated from oxidative addition to the carbonates is an important feature. As in the

<sup>34</sup> Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, 29, 5155.

<sup>35</sup> Sumida, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, 10, 1629.

palladium-catalyzed allyl-allyl cross coupling reaction, the primary difficulty generally associated with Ni-catalysis is still the lack of regiocontrol. Because 1,3-diene by-products are not formed, Ni is superior to Pd in terms of preventing  $\beta$ -H elimination.

**Scheme 2.18**



Copper-mediated reactions, especially allylic substitutions are of great importance in organic synthesis. Generally these reactions happen in a  $S_N2'$  fashion, delivering  $\gamma$ -substituted adducts in high regioselectivity. As an exception for this generalization, Cu-catalyzed allylation through the use of allylmethyl reagents is much less regioselective. It often delivers  $S_N2$  products, and also suffers from undesired homocoupling, thus is less investigated. Under carefully manipulated conditions homocoupling can be avoided, such as the example shown in equation 1 (Scheme 2.19): the CuI-catalyzed cross-coupling between allylic chlorides and allylic Grignards did not deliver dimers of substrates, however, only linear products were observed.<sup>36</sup> With self-activated allylsilane reagents (e.g. **2.59**), dimerization of substrates does not occur either, furnishing only the synthetically useful  $S_E2'$  products; allylic electrophiles bearing  $\gamma$ -substituents were not

<sup>36</sup> Erdic, E. *Tetrahedron* **1984**, 40, 641.

examined (equation 2).<sup>37</sup> To further understand the reaction with the hopes of improving the reaction in the future, the Bäckvall group has carried out mechanistic studies utilizing diallylcuprate species.<sup>38</sup> Their experimental data suggests that the Cu-catalyzed allyl-allyl coupling between allylic esters and allylic Grignard reagents proceeds with triallyl-Cu(III) complexes (**2.XI**, Figure 1.1) as the key intermediates, with the three allyl groups being pseudo-equivalent. Thus, the mixed 1,5-dienes are generated through non-chemoselective reductive elimination. Based on this argument, one can still not rule out the direct displacement mechanism that may be responsible for allylhalide substrates, since no homocoupling is detected.

#### Scheme 2.19

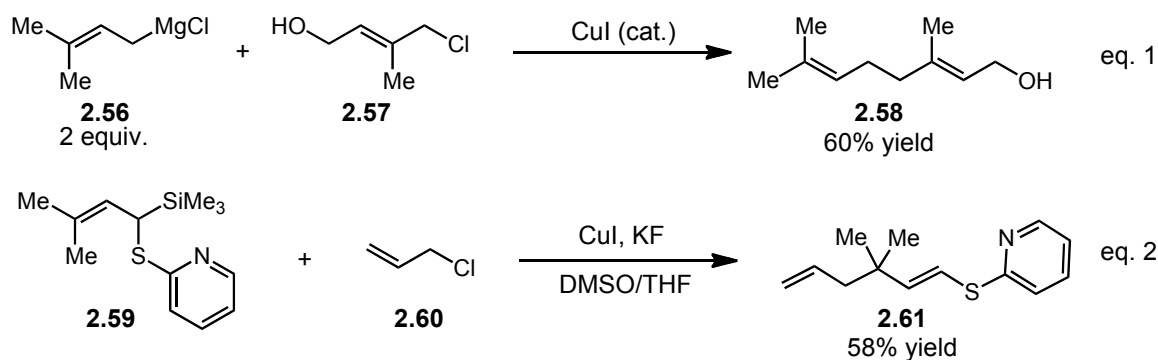
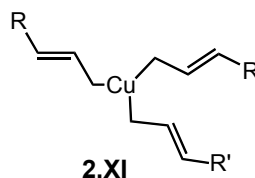


Figure 1.1



<sup>37</sup> Takeda, T.; Uruga, T.; Gohroku, K.; Fujiwara, T. *Chem. Lett.* **1999**, 821.

<sup>38</sup> Sofia, A.; Karlström, E.; Bäckvall, J. *Chem. Eur. J.* **2001**, 7, 1981.

Further studies in intramolecular allyl-allyl cross-couplings have realized cationic Au(I) complexes as more efficient catalysts.<sup>39</sup> The bifunctional substrates bearing allyl acetates and allylstannanes can undergo smooth cyclization by promotion from Au while completely inert under Pd-catalysis, through a mechanism that is believed to be quite different from that catalyzed by Pd(0) or Rh(I). In the mechanism proposed by the authors, Au(I) acts as a mild and selective Lewis acid that promotes formation of an allyl cation from the allyl acetate, which then reacts with the allylstannane or allylsilane. Both five-membered and six-membered carbocycles are synthesized.

#### IV. CONCLUSION

Although metal-catalyzed cross-coupling between organic electrophiles and allyl metals reagents has been studied, general regio- and stereoselective methods have not yet been realized. Due to the difficulties associated with allyl metal reagents, especially the lack of regiocontrol during the transformations, studies of these transformations are limited. For allyl-allyl coupling in particular, the use of allyl metal reagents can not be avoided and more effort is required to develop efficient transformations to construct synthetically useful 1,5-dienes.

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<sup>39</sup> Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarrren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1863.

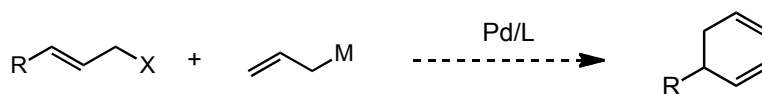
# Chapter III

## Palladium-Catalyzed Branch- and Enantioselective Allyl-Allyl Cross-Coupling

### I. INTRODUCTION

Enantioenriched 1,5-dienes could provide access to complex organic structures. With appropriate functionalization of the alkene moieties and with high levels of diastereocontrol, stereo-defined complex organic molecules can be obtained from the simple enantiomerically enriched dienes. Though they are attractive intermediates, to the best of our knowledge, optically active 1,5-dienes are not easily synthesized from readily accessed starting materials. The regio- and enantioselective cross-coupling between allylmetals and allylelectrophiles would be an ideal strategy to accomplish this (Scheme 3.1). However, as described in last chapter, due to the inherent instability associated with allylmetal reagents, together with lack of appropriate regiocontrol during the allylation, the metal-catalyzed allyl-allyl cross-couplings to date are unreliable for the synthesis of chiral 1,5-dienes

**Scheme 3.1**



## II. 3,3'-REDUCTIVE ELIMINATION OF BIS(ALLYL)PALLADIUM SPECIES

**A. Theoretical Studies.** Bis(allyl)palladium complexes are believed to be involved in some synthetically useful transformations. Schwartz's preliminary study on bis(allyl)Pd complexes has suggested carbon-carbon bond can form between the two allyl ligands through ligand promoted reductive elimination.<sup>1</sup> The Echavarren group has reported the Pd-catalyzed intramolecular allyl-allyl coupling for the synthesis of five- and six-membered-carbocycles;<sup>2</sup> this intramolecular Stille coupling is stereoselective, regardless of the isomeric forms of the starting materials, presumably resulting from the fact that all the isomers share a common intermediate, which is likely the bis(allyl)palladium complex.

The possible pathways leading to the formation of carbon-carbon bonds by the reductive elimination of bis(allyl)palladium complexes have been studied by the Echavarren group through the use of density functional theory (DFT) calculations.<sup>3</sup> Since both coordination modes ( $\eta^1$  and  $\eta^3$ ) for the two allyl ligands are possible, with several Pd(II) species in equilibrium, all three types<sup>4</sup> of bis(allyl)palladium complexes and their activation energies for the different modes of reductive elimination were investigated.

The DFT studies revealed three key aspects of the reductive elimination of the bis(allyl)palladium species:

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<sup>1</sup> Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, 21, 2599.

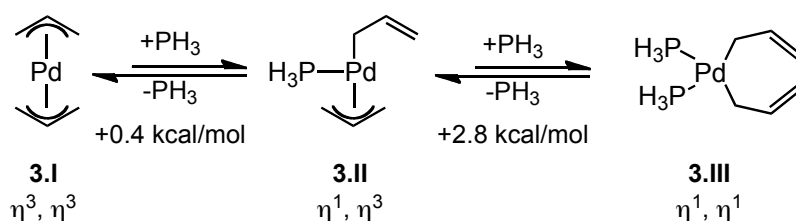
<sup>2</sup> Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, 8, 3620.

<sup>3</sup> Cárdenas, D. J.; Echavarren, A. M. *New. J. Chem.* **2004**, 28, 338.

<sup>4</sup> When the two allyl ligands are equivalent, there are three possible complexes in total.

1. The ground state energies of the Pd(II) species changes as phosphine ligands are added or removed. Complex **3.I** is most stable, with both allyl ligands in the  $\eta^3$ -binding mode. As illustrated in Scheme 3.2, the three 16-electron palladium complexes were compared in energy, revealing that there is 0.4 kcal/mol energy cost when one phosphine ligand associates with Pd(II) and more energy is needed (2.8 kcal/mol) for the binding of a second phosphine ligand.

**Scheme 3.2**



2. The reductive elimination from bis( $\eta^3$ -allyl)palladium **3.I** is a high-energy process ( $E_a = 36.6$  kcal/mol), which is in accordance with the experimental observations from several research groups.<sup>5</sup>

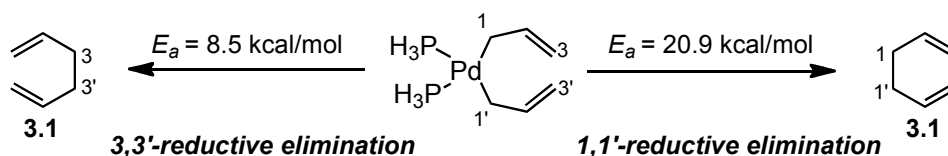
3. The paths requiring the lowest activation barriers correspond to the reductive eliminations from bis( $\eta^1$ -allyl)palladium complex (**3.III**). Among the possible transition states including the three types of carbon-carbon forming elimination (C1-C1', C1-C3, C3-C3') and two possible arrangements involved in C3-C3' (*syn* and *anti*), the formation of a bond between C3 and C3' is significantly preferred ( $E_a = 8.5$  kcal/mol), regardless of

<sup>5</sup> (a) Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028. (b) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1984**, *41*, 5779. (c) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779. (d) Nakamura, K.; Aoyagi, K.; Shim, J.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (e) Szabó, K. *J. Chem. Eur. J.* **2000**, *6*, 4413.



the *syn* and *anti* arrangements of the two allyl ligands (*anti* is favored by 2.6 kcal/mol). By comparison, the value of the corresponding C1-C1' reductive elimination is much higher ( $E_a = 20.9$  kcal/mol) (Scheme 3.3).

**Scheme 3.3**



Further theoretical studies of ligand effects on 3,3'-reductive elimination calculated by Espinet revealed that activation energies are greatly affected by the ligands bound to the metal center, meaning that the electronic properties of Pd are transmitted to the distal C3 and C3' carbons.<sup>6</sup> A metallopericyclic reaction was thus suggested to operate for the 3,3'-reductive elimination of *cis*-[Pd( $\eta^3$ -allyl)<sub>2</sub>L<sub>2</sub>] due to the structural, energetic and electronic similarities with the homo-Cope rearrangement.

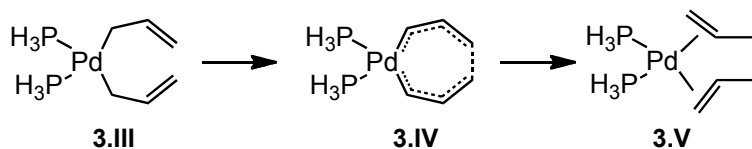
**B. The Origins for the Preference of 3,3'-Reductive Elimination.** Although the origins for the low activation barrier of 3,3'-reductive elimination has not been investigated in depth by experimental studies, there are two aspects we suspect to be responsible for this unique reactivity:

1. Natural bond orbital (NBO) analysis of transition states by Echavarren revealed that the preference for the 3,3'-reductive elimination is related to the interaction of the emerging double bonds between C1-C2 and C1'-C2' carbons with palladium.<sup>2</sup> Interaction

<sup>6</sup> Pérez-Rodríguez, M.; Braga, A. A. C.; de Lera, A. R.; Maseras, F.; Álvarez, R.; Espinet, P. *Organometallics* **2010**, 29, 4983.

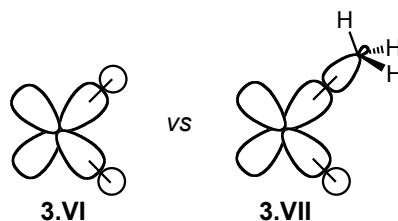
of the incipient  $\pi$ -clouds with one of the Pd lone pairs stabilizes these species. (Scheme 3.4)

**Scheme 3.4**



2. Theoretical studies by Goddard and co-workers on the reductive elimination of bis $\text{R}^1\text{R}^2$ (phosphine)palladium complexes ( $\text{R}^1$  or  $\text{R}^2 = \text{H}$  or  $\text{CH}_3$ ) to yield H-H, C-H or C-C bonds have realized a clear trend in activation barriers for the three types of couplings: H-H (2 kcal/mol) < H-C (10 kcal/mol) < C-C (23 kcal/mol).<sup>7</sup> The origin for the dramatic differences is believed to be in the H 1s and C  $\text{sp}^3$  orbitals. Since the H 1s orbital is spherical, it can simultaneously overlap with the Pd d orbital and the valence orbital of the other R group (3.VI, Figure 3.1). However when  $\text{R}^1$  or  $\text{R}^2 = \text{CH}_3$ , in order to form the new C-H or C-C bond, the orientation of  $\text{CH}_3$  is required to change thus leading to significant barriers (3.VII).

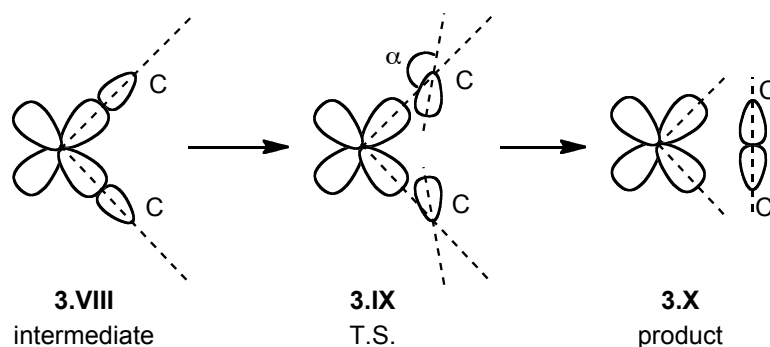
**Figure 3.1**



<sup>7</sup> Low, J. J.; Goddard, W. A., III; *J. Am. Chem. Soc.* **1986**, 108, 6115.

The orbital orientation effects have also been employed to explain the origins for the distinct C-C bond formation barriers in Pd-catalyzed Me-Me and vinyl-vinyl couplings.<sup>8</sup> Through DFT calculations, it was found that Me is much more sensitive towards the orbital orientation change, with 25.6 kcal/mol increasing in energy upon decreasing the  $\alpha$  angle from 180 to 130 (in the model system  $\text{MePd}(\text{PH}_3)_2^+$ ,  $\alpha$  angle see **3.IX**, Scheme 3.5). For vinyl, this energy is only 10.0 kcal/mol. The sensitivity to the orientation change in the model systems is in accordance with the calculated activation barriers for the two types of coupling (Me-Me:  $E_a = 25.2$  kcal/mol, vinyl-vinyl:  $E_a = 6.8$  kcal/mol), suggesting the kinetics of C-C bond formation is greatly affected by the orientation change.

**Scheme 3.5**



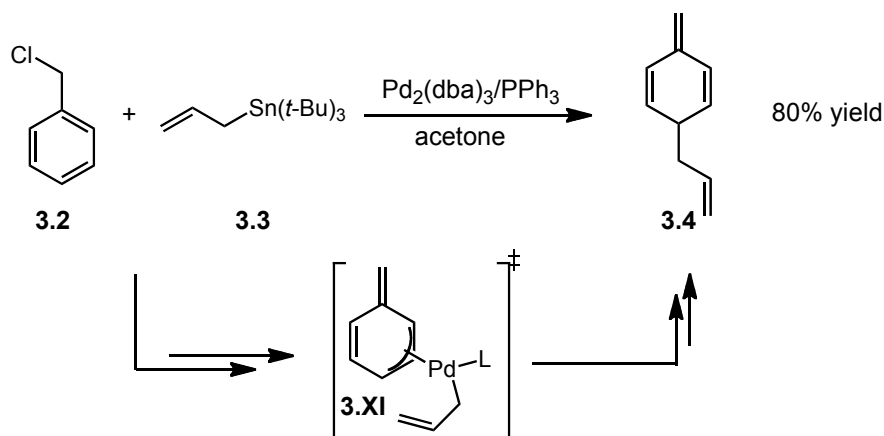
According to above two experiments, we envisioned that since 1,1'-reductive elimination requires two  $\text{sp}^3$  hybridized carbons (C1 and C1') to adjust their orbital orientations during the transition state, high activation barrier would be generated. On the other hand for 3,3'-reductive elimination, a new carbon-carbon bond forms at the distal

<sup>8</sup> Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *Organometallics* **2005**, 24, 715.

carbons (C3 and C3') where two  $sp^2$  carbons interact efficiently without significant orbital reorientation, therefore this process is likely be more favorable.

**C. Experimental Observations In Support of 3,3'-Reductive Elimination.** In addition to the examples discussed in Chapter I, 3,3'-reductive elimination has also been observed in several other carbon-carbon and carbon-hetero atom bond formations where allyl-metal complexes are involved. The palladium-catalyzed coupling between benzyl chloride with allyltributylstannanes leads to an unexpected dearomative allylation product, as reported by the Yamamoto group.<sup>9</sup> DFT calculations by Liu and Avriaferd of the reaction mechanism suggest a reductive elimination between the *para* carbon of the aromatic ring and the C3 of the allyl ligand, from the  $(\eta^3\text{-benzyl})(\eta^1\text{-allyl})$ palladium complex (**3.XI**).<sup>10</sup>

**Scheme 3.6**

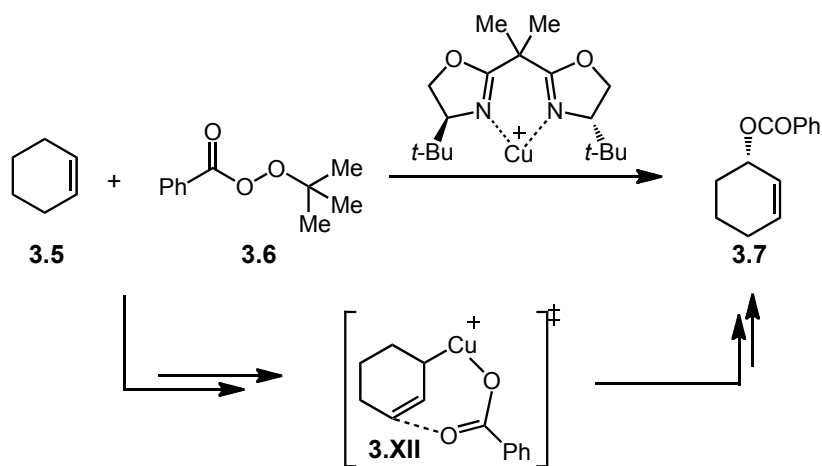


<sup>9</sup> Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, 123, 759.

<sup>10</sup> Ariaferd, A.; Liu, Z. *J. Am. Chem. Soc.* **2006**, 128, 13010.

The copper-catalyzed allylic oxidation of alkenes with *tert*-butyl perbenzoate (the Kharasch–Sosnovsky Reaction) is a powerful transformation for the functionalization of simple alkenes, resulting in enantioenriched allylic esters when appropriate chiral ligands are employed. The carbon-oxygen bond is proposed to be formed through the stereospecific reductive elimination of the allyl-copper(III) complexes involving  $\pi$ -bond migration.<sup>11</sup> (Scheme 3.7)

**Scheme 3.7**

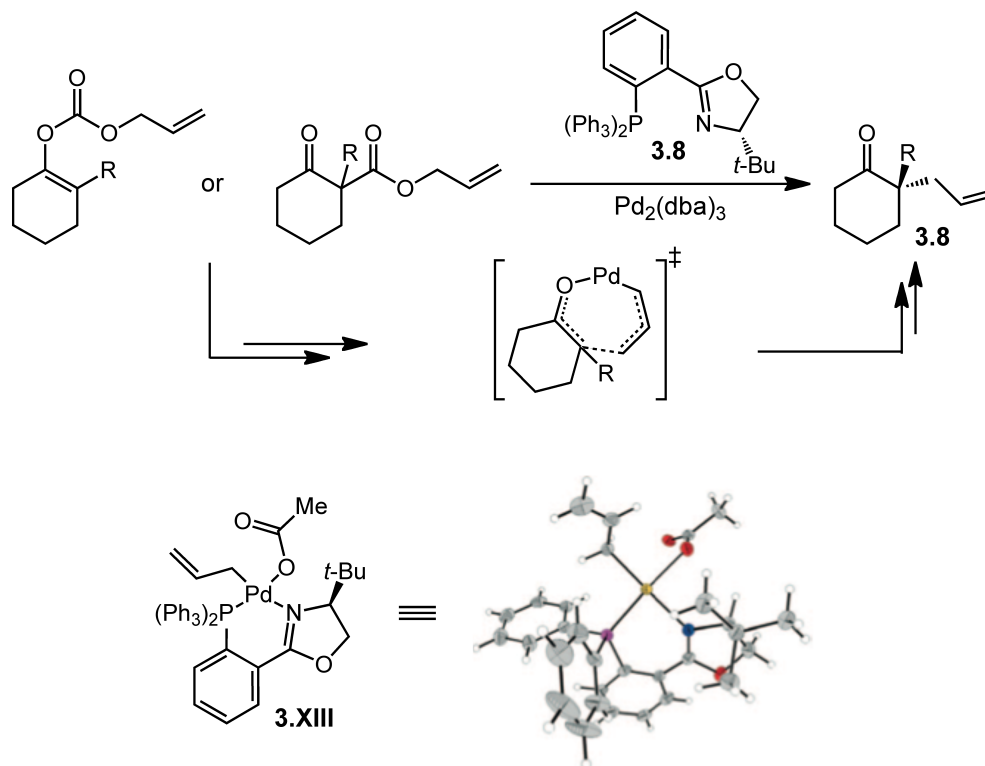


The 3,3'-reductive elimination is also believed to be responsible for the decarboxylative Tsuji allylation. Although enolates are normally considered as soft nucleophiles and attack palladium- $\pi$ -allyl complexes through an outer sphere pathway, DFT calculations done by Stoltz group indicate the reductive elimination of an ( $\eta^1$ -allyl)(O-enolate)palladium furnishing the desired carbon-carbon bond is much more

<sup>11</sup> (a) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, 58, 845. (b) Mayoral, J. A.; Rodríguez-Rodríguez, S.; Salvatella, L. *Chem. Eur. J.* **2008**, 14, 9274.

favorable based on the low activation energy.<sup>12</sup> X-ray crystal structure analysis of the acetate analogue (**3.XIII**) implicates a square planar complex, structurally similar that required for 3,3'-reductive elimination.<sup>13</sup> (Scheme 3.8)

**Scheme 3.8**



More recently,  $\alpha$ -carbanions of imines have been reported as nucleophiles in the Pd-catalyzed allylic alkylation of allyl halides, affording ketone products upon hydrolysis (Scheme 3.9).<sup>14</sup> According to experimental mechanistic studies and DFT calculations, the

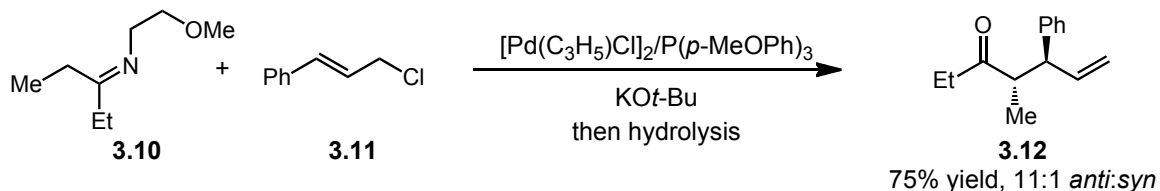
<sup>12</sup> (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

<sup>13</sup> Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840.

<sup>14</sup> Chen, J.; Peng, Q.; Lei, B.; Hou, X.; Wu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 14180.

excellent selectivity for the  $S_N2'$  product is believed to rely on an inner sphere 3,3'-reductive elimination of the  $(\eta^1\text{-allyl})(\text{N-enamine})\text{palladium(II)}$  complexes.

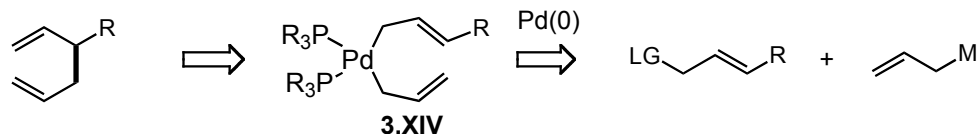
### Scheme 3.9



## III. THE DEVELOPMENT OF PALLADIUM-CATALYZED ALLYL-ALLYL CROSS-COUPLING

**A. Discovery of Branch-Selective Allyl-Allyl Cross-Coupling.** While developing the Ni-catalyzed allylation of dienals, it was envisioned that 3,3'-reductive elimination could potentially facilitate a branch selective allyl-allyl cross-coupling. In a bis(allyl)metal complex such as **3.XIV** (Scheme 3.10), where one allyl ligand bears a substituent on the C1 or C3 carbon, we anticipated the R group would prefer to be distal from the metal center to avoid steric interactions. If the activation energy is still lower than the competing 1,1'-coupling regardless of the substituent, 3,3'-reductive elimination would generate the branched 1,5-dienes during carbon-carbon bond formation. It was envisioned that **3.XIV** could be generated by the treatment of allylic electrophiles and suitable allylmetal reagents with palladium(0) precursors.

### Scheme 3.10



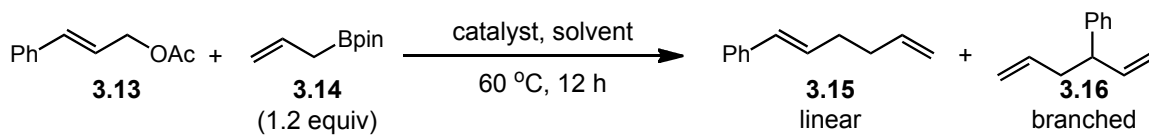
Cinnamyl acetate was chosen as a test substrate since it is known to undergo smooth oxidative addition with Pd(0) complexes. AllylB(pin) was used as the nucleophile because this commercially available, relatively nontoxic, air stable allylmetal reagent has proven reactive with Pd(II) complexes.<sup>15</sup> The two starting materials were heated in several organic solvents along with a variety of metal catalysts. As shown in Table 3.1, Pd<sub>2</sub>(dba)<sub>3</sub>/PPh<sub>3</sub> represents the most active catalyst in THF, with which, cinnamyl acetate fully converts after a 12-hour period. Pt and Ni are not as efficient in promoting this coupling reaction.

The major product was determined to be (*E*)-hexa-1,5-dien-1-ylbenzene (**3.15**), the linear product of the allyl-allyl cross-coupling; in some cases a small amount of cinnamyl-cinnamyl dimer (e.g. entries 2-5) were formed. Under the catalysis system shown in entry 5, the linear product was isolated in 68% yield. Although this is not the product we expected, the substrate was fully converted leaving open the possibility of tuning the conditions to favor the branched products.

<sup>15</sup> For representative examples: (a) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, 37, 6889. (b) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, 129, 2214.



**Table 3.1 Initial Studies of Reaction Conditions**



entry	catalyst	solvent	%conv. <sup>a</sup>	L:B <sup>a</sup>
1	2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	THF	<5	n/a
2	2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub> , 5 mol % PPh <sub>3</sub>	THF	72 <sup>b</sup>	>95:5
3	2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub> , 5 mol % PPh <sub>3</sub>	MeCN	25 <sup>b</sup>	>95:5
4	2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub> , 5 mol % PPh <sub>3</sub>	PhMe	56 <sup>b</sup>	>95:5
<b>5</b>	<b>5 mol % Pd<sub>2</sub>(dba)<sub>3</sub>, 10 mol % PPh<sub>3</sub></b>	<b>THF</b>	<b>&gt;95<sup>b</sup></b>	<b>&gt;95:5</b>
6	5 mol % Pd <sub>2</sub> (dba) <sub>3</sub> , 10 mol % PCy <sub>3</sub>	THF	84	>95:5
7	5 mol % Pt <sub>2</sub> (dba) <sub>3</sub> , 10 mol % PPh <sub>3</sub>	THF	n/a	>95:5
8	10 mol % Ni(cod) <sub>2</sub> , 10 mol % PCy <sub>3</sub>	THF	10	>95:5
9	10 mol % Ni(cod) <sub>2</sub> , 20 mol % PCy <sub>3</sub>	THF	10	>95:5

<sup>a</sup> Conversion and L:B ratio determined by <sup>1</sup>H NMR analysis of unpurified reaction mixture. <sup>b</sup> Dimerization of cinnamyl acetate observed in unpurified reaction mixture.

Although it is still not clear how the linear product arises during Pd-catalyzed reaction of cinnamyl acetate and allylB(pin), based on the possible Pd-allyl complexes **3.XV**, **3.XVI**, **3.XVII** and **3.XVIII**, there are four plausible routes (Scheme 3.11):

Path a: perhaps due to the steric bulk of two triphenylphosphine ligands, or due to the congestion around the substituted C3 in **3.XV**, the 3,3'-reductive elimination is not favored. Instead, a new bond forms between C1 and C1' as these carbons are compressed by the ligands on Pd.

Path b: complex **3.XVI** may form during the catalytic cycle, where the L could be another phosphine ligand, or an empty site as a result of the steric buck generated by the phenyl group on C1 carbon. Although **3.XVI** is probably less favored than **3.XV** due to significant steric interaction between Ph and Pd-ligand complex, 3,3'-reductive elimination would more likely occur from **3.XVI** according to the Curtin-Hammett principle. This pathway is also supported by Espinet's DFT calculations,<sup>6</sup> which suggests that when L is an empty site, 3,3'-reductive elimination has the lowest activation energy among all the tested ligands (including PMe<sub>3</sub>, maleic anhydride and ethylene).

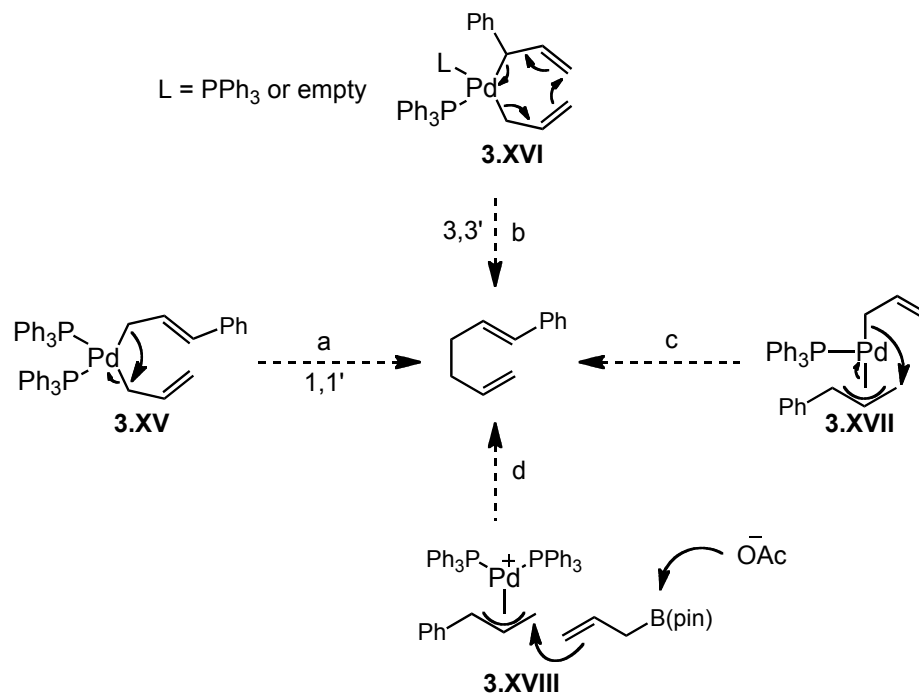
Path c: as calculated by Echavarren,<sup>3</sup> the equilibrium between **3.XV** and **3.XVII** favors **3.XVII**. Therefore, the linear product could be generated from the ( $\eta^1$ -allyl)( $\eta^3$ -allyl)(PPh<sub>3</sub>)palladium where reductive elimination happens at the less hindered carbon of the  $\eta^3$ -allyl ligand. According to Espinet,<sup>6</sup> this pathway is, in fact, lower energy than the 1,1'-reductive elimination.

Path d: repeats an outer sphere coupling that has been proposed for the allylic allylation between allyl acetates with allylstannanes<sup>1,2</sup> and allylsilanes.<sup>16</sup> Upon formation of the  $\pi$ -allyl-palladium complex **3.XVIII**, instead of transmetalation with Pd(II), allylB(pin) directly attacks the  $\eta^3$ -allyl ligand in the same manner as soft nucleophiles, presumably with activation from *in situ* generated acetates.

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<sup>16</sup> Hatanaka, Y.; Ebina, Y. Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

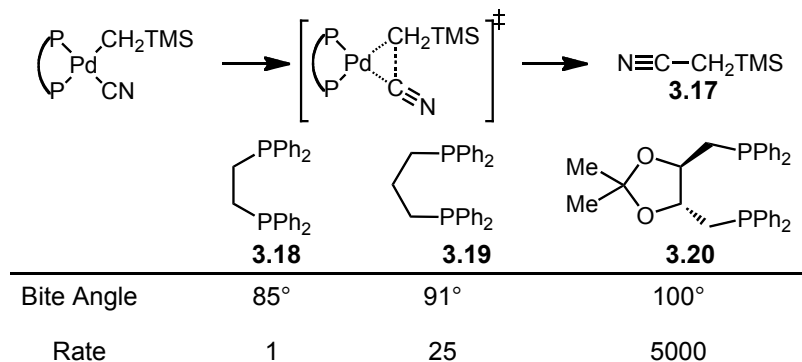
**Scheme 3.11**



According to the above analysis, we hoped to invert the regioselectivity by replacing triphenylphosphine with a bidentate ligand. With the two phosphines tethered together, we envisioned that the **3.XVII** analogues would not be formed since Pd(II) prefers to be a 4-coordinate square planar complex. More importantly, it has been shown by Moloy that the rate of C1-C1' reductive elimination is significantly affected by diphosphine bite angles.<sup>17</sup> That is by increasing the bite angle, the  $\angle \text{CPdC}$  compresses and the distance between C1 and C1' decreases; the carbon-carbon bond formation is thereby accelerated, so as to promote reductive elimination (Scheme 3.12).

<sup>17</sup> Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, *120*, 8527.

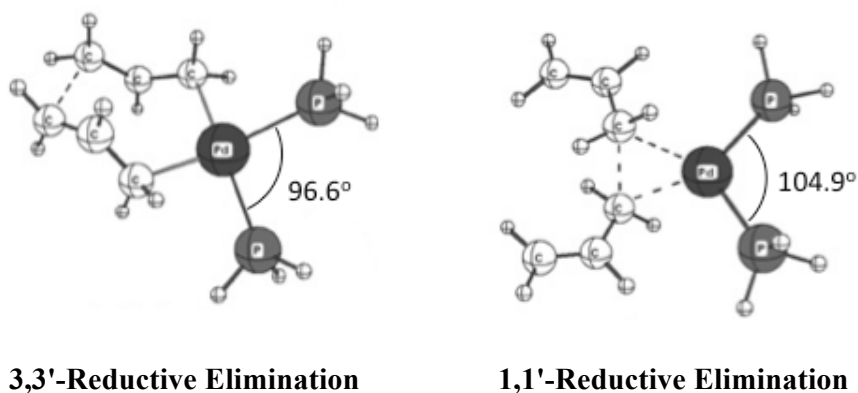
**Scheme 3.12**



While bite angle effects weren't discussed by Echavarren, we extracted that the P-Pd-P angles from his calculated transition state coordinates. As demonstrated in Figure 3.1, the calculated transition structure for 1,1' and 3,3' reductive eliminations from bis( $\eta^1$ -allyl)(PH<sub>3</sub>)<sub>2</sub>palladium exhibit P-Pd-P angles of 104.9° and 96.6°, respectively, suggesting that diphosphine ligands bearing smaller bite angles may favor the new bond forming at the distal carbons.<sup>18</sup> (Figure 3.2)

**Figure 3.2:**

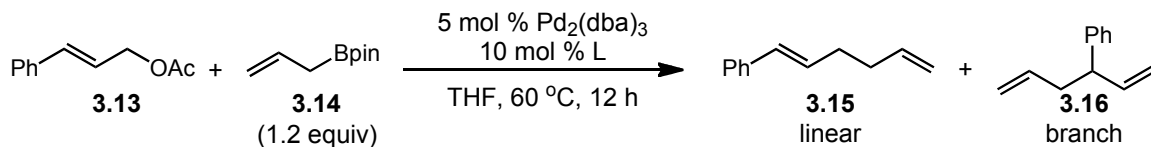
**The  $\angle$ PPdP in the DFT Calculated T.S. for the 1,1' and 3,3' Reductive Eliminations.**



<sup>18</sup> See the supporting information for reference 3.

Gratifyingly, upon the evaluation of a panel of bidentate phosphine ligands, the coupling between cinnamyl acetate and allylB(pin) yielded the desired branch product (**3.16**) to varying degrees. As we expected, the linear/branch ratio is substantially impacted by the bite angle, with small bite angle ligands delivering the branched coupling adduct exclusively (e.g. dpp-benzene and dppe), and the homodimer was not observed in either. In contrast, large bite angle ligands like dppb, dppf and DPEPhos afforded only linear 1,5-dienes (Table 3.2).

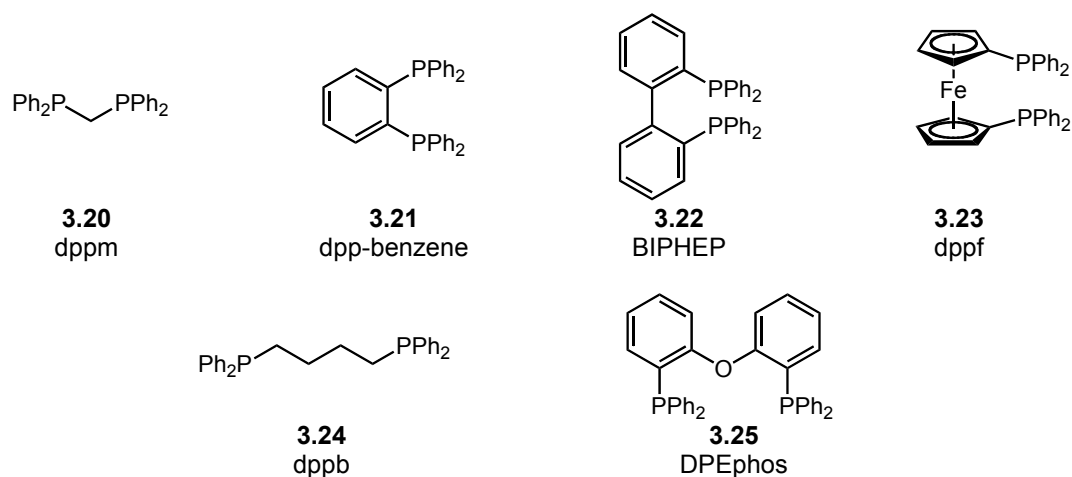
**Table 3.2 Evaluation of Bidentate Phosphine Ligands**



<b>L</b>	$\beta/^\circ$	%conv. <sup>a</sup>	<b>L:B</b> <sup>a</sup>
dppm	72	53 <sup>b</sup>	58:42
<b>dpp-benzene</b>	<b>83</b>	<b>35</b>	<b>5:&gt;95</b>
<b>dppe</b>	<b>85</b>	<b>25</b>	<b>5:&gt;95</b>
BIPHEP	~90	<5	n/a
dppp	91	<5	n/a
dppf	96	43	>95:5
dppb	98	70	>95:5
DPEphos	102	41	>95:5

<sup>a</sup> Conversion and L:B ratio determined by  $^1\text{H}$  NMR analysis of unpurified reaction mixture. <sup>b</sup> 22% of the unpurified mixture is the dimer of substrate.

**Figure 3.3 Achiral Biendate Phosphine Ligands**

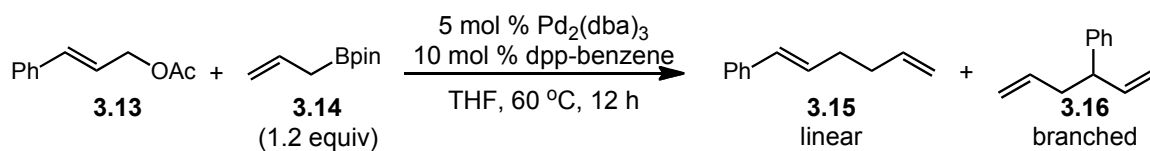


Although the branch-selective allyl-allyl cross-coupling is achieved by through the use of suitable bidentate ligands, the reaction is not efficient, only 35% and 25% of substrate converted during a 12-hour reaction when employing highly branch-selective ligands dpp-benzene and dppe, respectively (Table 3.2). We rationalized that since cinnamyl acetates have been well documented to oxidatively add to the Pd(dppe)-type of complexes,<sup>19</sup> the low conversion of the coupling may be a result of either slow transmetallation or reductive elimination. Reductive elimination, in general, is substantially affected by the electronic and steric nature of the coupling groups on the metal as well as by the phosphine ligands. To obtain high regioselectivity in the allyl-allyl cross-coupling, we already appear to require specific ligands, thus manipulating the electronics and sterics of the bidentate ligands may not be most productive. It has been shown that the Lewis acidity of allylB(pin) is low compared to its boronic ester

<sup>19</sup> Representative example of cinnamyl acetate reacting under Pd(dppe) catalysis: Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, 53, 3845.

analogues, due to the strong electron donating from the oxygen lone pairs. Thus strong activation may be required for higher reactivity. In fact, in the allyl-aryl Suzuki coupling described by Podestá, the transmetallation of allylB(pin) was activated by strong base *sec*-BuLi.<sup>20</sup> Therefore, in the Pd-catalyzed allyl-allyl coupling, where the branch-selectivity is ensured by dpp-benzene, basic additives were employed to accelerate transmetallation and enhance the reaction efficiency. As shown in Table 3.3, bases indeed proved beneficial, with 3 equivalents of Cs<sub>2</sub>CO<sub>3</sub> providing 75% yield of the desired branch product (**3.16**) and full substrate conversion reaction. Strongly nucleophilic bases, such as potassium *tert*-butoxide, caused the reactants to completely decompose.

**Table 3.3 Evaluation of Base Additives**



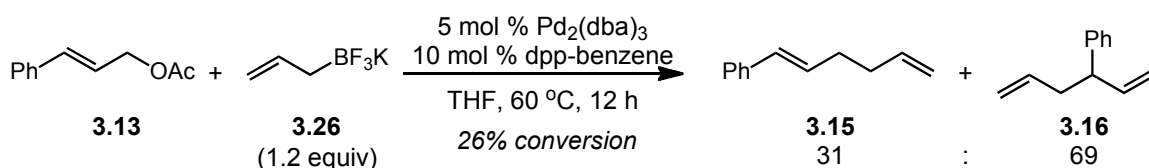
Additive	%conv. <sup>a</sup>	B:L <sup>a</sup>	%yield <sup>b</sup>
LiCl (3 equiv)	6	>95:5	n/a
KF (3 equiv)	58	>95:5	34
K <sub>2</sub> CO <sub>3</sub> (3 equiv)	87	>95:5	51
Cs <sub>2</sub> CO <sub>3</sub> (3 equiv)	>95	>95:5	75
KO <sup>t</sup> Bu (3 equiv)	decomp.	n/a	n/a

<sup>a</sup> Conversion and B:L ratio determined by <sup>1</sup>H NMR analysis of unpurified reaction mixture. <sup>b</sup> Yield of purified product.

<sup>20</sup> Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, 3964.

Inspired by Miyaura work,<sup>21</sup> in which allyltrifluoroborates exhibit excellent reactivity as organometal reagents in Pd(0)-catalyzed cross-couplings, this class of allylboron reagents was investigated in allyl-allyl coupling. As shown in Scheme 3.13, by employing **3.26**, the reaction not only suffers from low conversion, the high regiocontrol from the optimal bidentate ligand dpp-benzene loses its power as well. Therefore allylB(pin) was employed in further studies.

**Scheme 3.13**



**B. Enantioselective Allyl-Allyl Cross-Coupling.** With the effective means to control the site selection and achieve excellent branch-selection, as well as to enhance the reaction efficiency by the addition of appropriate bases, it was of great interest to achieve enantiocontrol during the transformation as well. A general approach in metal-catalysis is to engage a chiral ligand, which binds to the metal center creating a chiral environment which transfers its chiral information to the reaction product. Although enantioselective allyl-allyl cross-coupling has not been reported, and one may worry about the effectiveness of the enantiocontrol by the ligand far away from C3 and C3', success of enantioselective conjugate allylation and allylation of dienals as discussed in Chapter I,

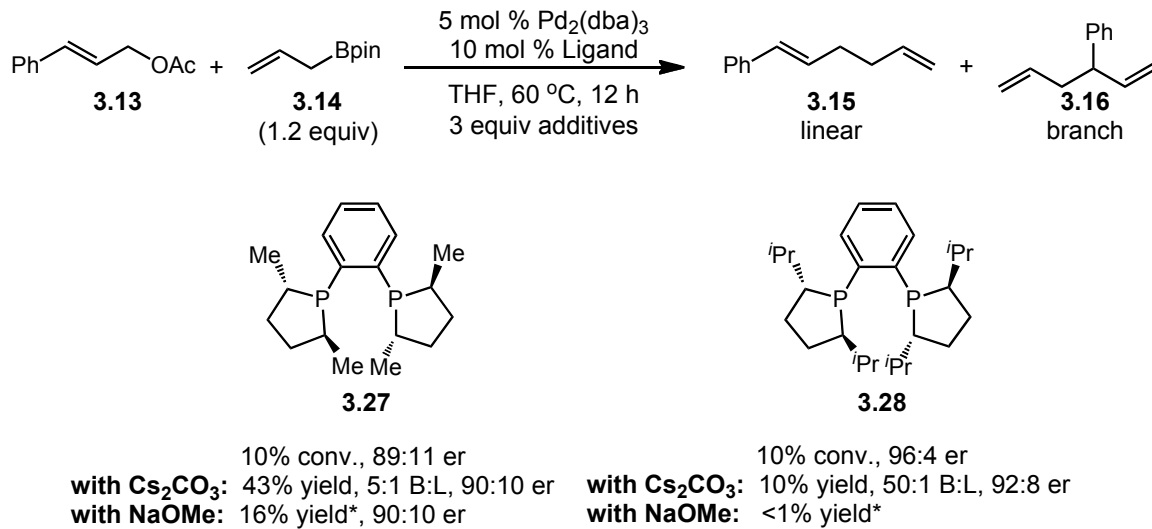
<sup>21</sup> (a) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, 35, 704. (b) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, 35, 1368. (c) Yamamoto, Y.; Takada, S.; Miyaura, N. *Organometallics* **2009**, 28, 152.



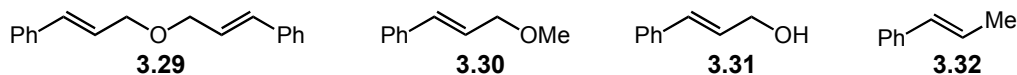
as well as the recent theoretical study by Espinet<sup>6</sup>, provided good reasons to pursue this goal.

Aiming to synthesize optically pure **3.16** through Pd-catalyzed allyl-allyl cross-coupling, chiral ligands bearing similar bite angles to that of dpp-benzene were initially examined. As described in Scheme 3.14, **3.16** can be synthesized in enantiomerically enriched form when DuPhos type ligands ( $\beta = 84^\circ$ ) were employed, yet the reactivities are low, only 10% conversion in both cases. The strategies to boost reaction efficiency by through the use of base additives proved beneficial in a ligand dependent manner, with Me-Duphos (**3.27**) delivering the desired product in much higher yield than *i*-Pr-Duphos (**3.28**). When sodium methoxide was employed, although the reaction went to full conversion, the products consisted of a variety of cinnamyl derivatives including two ethers (**3.29** and **3.30**), cinnamyl alcohol (**3.31**) and  $\beta$ -methylstyrene (**3.32**), while the yield of desired 1,5-diene is low. Thus adding bases to the reaction appeared not to be the ultimate solution for this ligand class.

**Scheme 3.14**



\* The low yield with NaOMe results from the formation of following by-products:



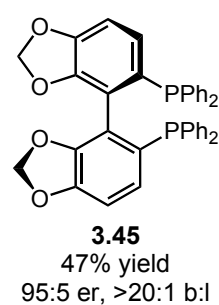
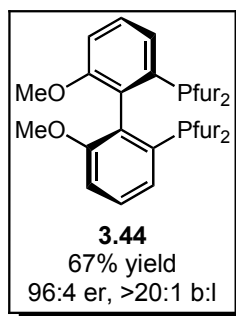
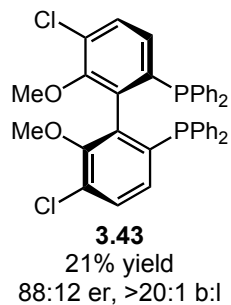
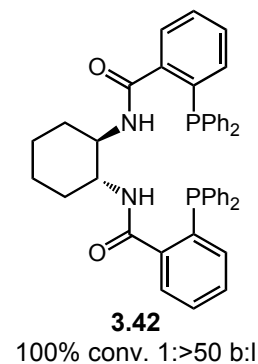
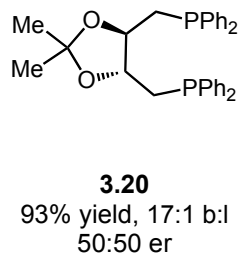
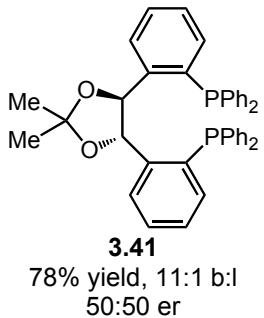
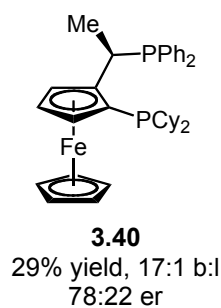
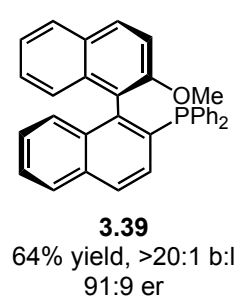
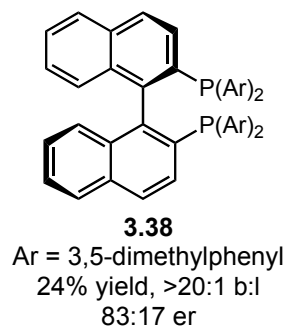
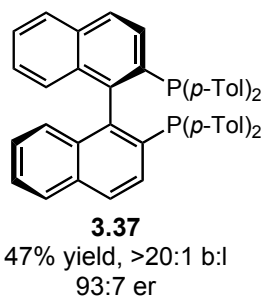
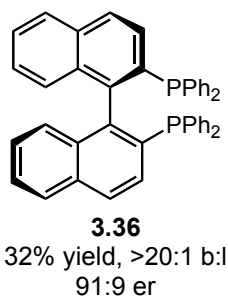
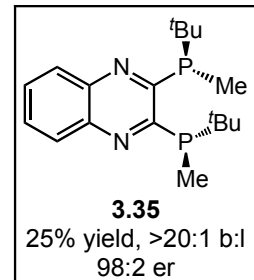
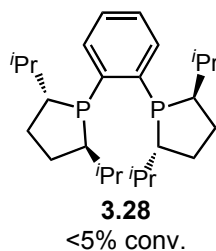
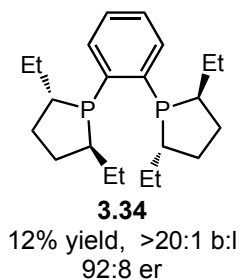
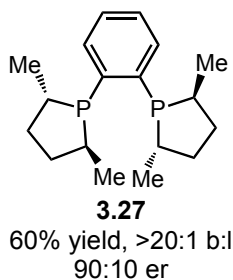
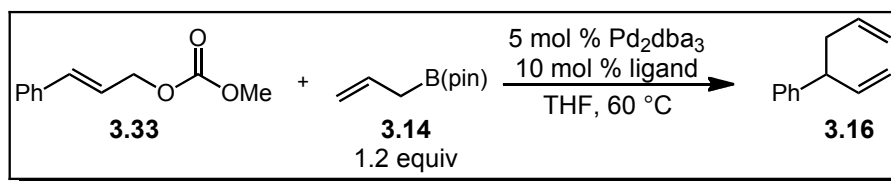
While the byproducts associated with the NaOMe additive are likely due to the reaction of the base with the Pd-allyl intermediates, it was postulated that if the base could be generated *in situ* in a catalytic amount, the reaction may benefit from the effective boron-base interaction without suffering from the undesired pathways. Cinnamyl methyl carbonate was then chosen as the substrate, which would slowly release a catalytic amount of methoxide as the carbonate leaving group expels CO<sub>2</sub>.

As demonstrated in Table 3.4, the allyl-allyl coupling is indeed improved by simply changing the substrate. Compared to the 10% conversion with cinnamyl acetate, the methyl carbonate analogue (**3.33**) affords the desired 1,5-diene in 60% yield and 90:10 er, under the same reaction conditions. With a superior substrate class in hand, a

series of chiral bidentate ligands were examined in order to identify the ligand that would provide high yield, regioselectivity and importantly, outstanding enantioselectivity during this transformation.

Among the DuPhos series (**3.27**, **3.28** and **3.34**), the enantiomeric purity of the product is dependent upon the steric bulk of the substituents on phosphorous, with bulkier groups providing higher selectivity but slowing the reaction. Following this trend, the sterically encumbered P-chiral ligand QuinoxP\* (**3.35**) was able to provide excellent enantiocontrol, delivering **3.16** in 98:2 er, yet only in 25% yield. The low yield is due to dimerization of cinnamyl carbonate. BINAP and its analogues (**3.37** and **3.38**) were also employed, for their bite angles fall into the desired range, but they were not advantageous compared to other ligands. One noteworthy observation is that when the aromatic group on phosphorous is changed from *para*-tolyl to 3,5-dimethylphenyl, enantioselectivity decreased significantly, which encouraged us to look at similar ligands that have smaller aryl substituents. To our delight, MeO-Fur-BIPHEP (**3.44**) proved exceptional in regiocontrol (>20:1 b:l), enantiocontrol (96:4 er) and reactivity (67% yield). However, there was still room to improve the efficiency since 25% of starting material was converted to cinnamyl methyl ether (**3.30**). In contrast, MORPHOS (**3.41**) and DIOP (**3.20**) failed to provide any enantiocontrol, yielding racemic mixtures of **3.16**. The Trost ligand (**3.42**) delivers only linear product, likely due to its long and flexible backbone and acting more like monodentate ligands in this reaction.

**Table 3.4 Evaluation of Chiral Ligands**



We were very close to the optimal condition for the enantioselective allyl-allyl cross-coupling: employing QuinoxP\* (**3.35**) or MeO-Fur-BIPHEP (**3.44**) as the optimal chiral ligands, however, reaction efficiency needed to be improved.

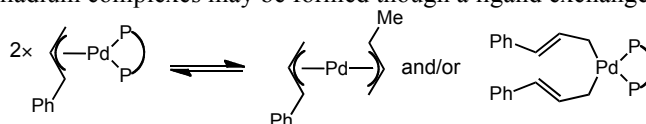
With regard to QuinoxP\* (**3.35**), the major problem is the cinnamyl-cinnamyl dimerization (**3.46**, **3.47** and **3.48**, Table 3.5). It is plausible that dimers are generated from the non-regioselective reductive elimination from bis(cinnamyl)palladium complexes, likely derived from the ligand exchange of two cinnamylpalladium complexes (transmetallation of allylB(pin) is not efficient).<sup>22</sup> Therefore, several experiments were carried out based on the above hypothesis (Table 3.5):

1. The reaction was diluted in order to lower the concentration of the cinnamylpalladium complexes. However, suppression of the dimerization was not observed (entry 2).

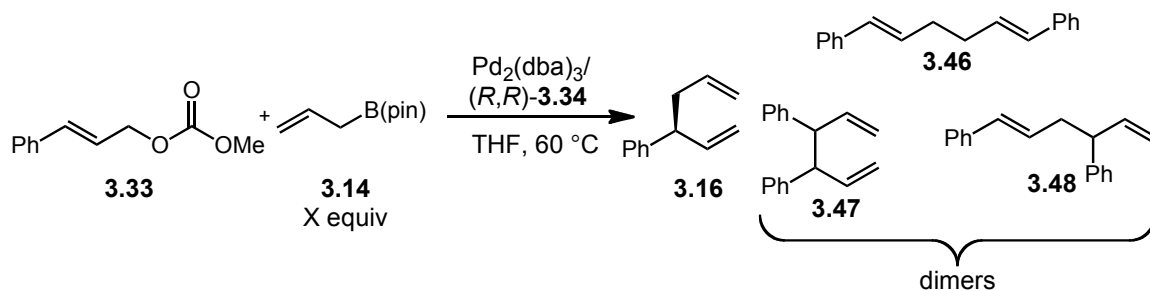
2. The amount of allylB(pin) was increased to enhance the rate of reductive elimination. This indeed enhanced reaction efficiency (entries 5-13).

3. Base additives that might accelerate transmetallation were examined. They improved the desired 1,5-diene formation over the dimerization in a concentration dependent manner. With 1 equivalent of Cs<sub>2</sub>CO<sub>3</sub>, **3.16** was isolated in 66% yield and excellent er (entry 8).

<sup>22</sup> The bis(cinnamyl)palladium complexes may be formed through a ligand exchange process:



**Table 3.5 Optimization of Reaction Condition with QuinoxP\***

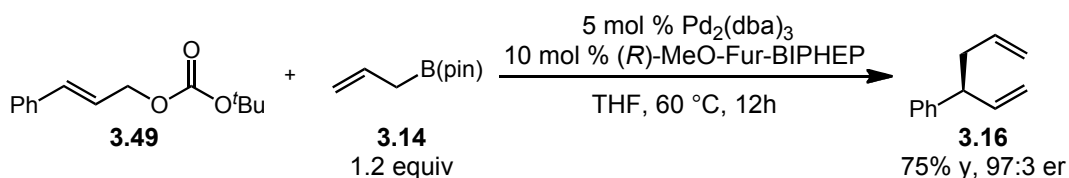


entry	additive	[substrate]	X	catalyst (mol % of 'Pd')	product: dimers <sup>a</sup>	%yield <sup>b</sup>
1	none	0.5 M	1.2	10	42:58	25
2	none	0.1 M	1.2	10	38:62	n/a
3	Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	0.5 M	1.2	10	76:24	34
4	EtOH (3 equiv)	0.5 M	1.2	10	51:49	n/a
5	Cs <sub>2</sub> CO <sub>3</sub> (3 equiv)	0.5 M	3	5	65:35	47
6	Cs <sub>2</sub> CO <sub>3</sub> (3 equiv) <sup>c</sup>	0.5 M	3	5	68:32	35
7	Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	0.5 M	3	5	68:32	n/a
8	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	0.5 M	3	5	78:22	66
9	Cs <sub>2</sub> CO <sub>3</sub> (0.5 equiv)	0.5 M	3	5	77:23	53
10	K <sub>3</sub> PO <sub>4</sub> (1.2 equiv)	0.5 M	3	5	76:24	42
11	NaOH (1.2 equiv)	0.5 M	3	5	75:25	45
12	NaOH (1.2 equiv, 1 M in H <sub>2</sub> O)	0.5 M	3	5	42:58	n/a
13	NaOH (1.2 equiv, 3 M in H <sub>2</sub> O)	0.5 M	3	5	62:38	n/a

<sup>a</sup>Product:dimers ratio determined by <sup>1</sup>H NMR analysis of unpurified reaction mixture. <sup>b</sup>Yield of purified product. <sup>c</sup>The reaction was run at r.t.

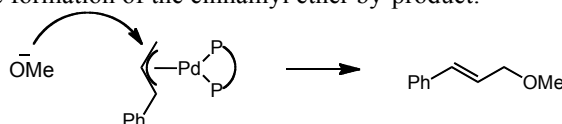
In contrast to QuinoxP\*, the problem associated with MeO-Fur-BIPHEP is the formation of cinnamyl methyl ether (**3.31**), likely as a consequence of the outer sphere attack of methoxide on to the cinnamylpalladium complex.<sup>23</sup> Thus a bulkier alkoxide such as *tert*-butoxide was considered as it might inhibit this process. As shown in Scheme 3.15, cinnamyl *tert*-butyl carbonate was used as the substrate. By employing a more sterically hindered carbonate, the efficiency of the Pd-catalyzed allyl-allyl cross-coupling was further improved, affording only minimal amounts of the ether byproduct and without diminishing the high regio- and enantioselectivity.

**Scheme 3.15**



Before examining the scope of the reaction with the optimized conditions, correlations between bite angles of the bidentate achiral ligands and the branch:linear selectivity were again studied because the initial investigation was based on the preliminary conditions wherein reactivities for many ligands were too low to deliver any product. The study of representative diphosphines under the optimal conditions is given in Table 3.6. Benefiting from the more nucleophilic alkoxide, allyl-allyl coupling under neutral condition is very efficient and effective, delivering 1,5-dienes in full conversion

<sup>23</sup> Plausible pathway for the formation of the cinnamyl ether by-product:



regardless of the ligands. A clear trend of the bite angle-mediated regiocontrol becomes clear: small bite angle ligands afford clean branch product and large bite angle ligands are non-selective, which is in agreement with the previous discussion on bite angle effects.

**Table 3.6 The Bite Angle Effect on the Regioselectivity**

Reaction scheme: 3.49 + 3.14 (1.2 equiv)  $\xrightarrow[\text{THF, 60 } ^\circ\text{C, 12 h}]{\text{5 mol \% Pd}_2(\text{dba})_3, \text{10 mol \% ligand}}$  3.16 + 3.15

L	$\beta_n^\circ$	%yield <sup>a</sup>	b:l <sup>b</sup>
PPh <sub>3</sub>	-	68	1:>20
dpp-benzene	83	70	97:3
dppe	85	77	98:2
dppp	91	80	97:3
dppf	96	43	94:6
dppb	98	77	38:62
DPEphos	102	58	72:28

<sup>a</sup> Yield of the isolated products. <sup>b</sup> Determined by <sup>1</sup>H analysis of the purified products.

### C. Scope of the Pd-Catalyzed Enantioselective Allyl-Allyl Cross-Coupling.

With the conditions for the Pd-catalyzed enantioselective allyl-allyl cross-coupling optimized, the scope of the reaction was surveyed. As shown in Table 3.7, the reaction is effective with a number of allylic carbonates bearing aromatic substituents, delivering the branched-product with excellent regioselectivity and generally high enantioselectivity. It is noteworthy that the racemic internal and the terminal carbonates can be used interchangeably, yielding 1,5-dienes in comparable levels of selectivities (entries 1 and

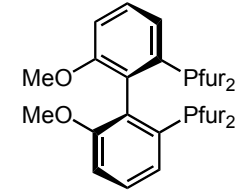
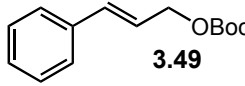
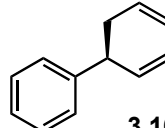
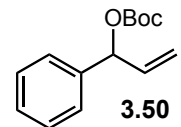
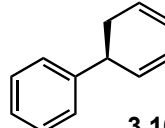
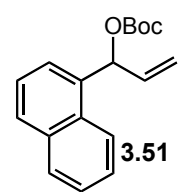
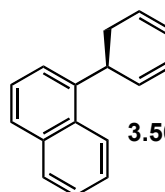
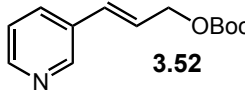
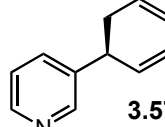
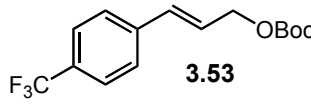
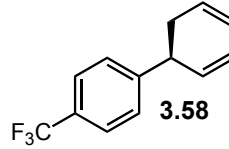
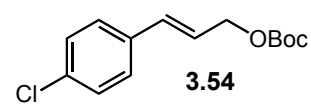
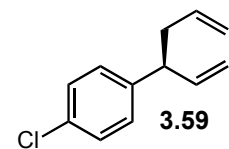
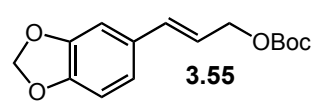
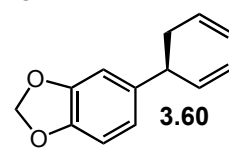


2). This observation has mechanistic implications and is also of practical importance: internal carbonates are easier to access than the corresponding terminal compounds. Sterically encumbered (**3.51**), halogenated (**3.54**), and oxygenated (**3.55**) aromatic allylic carbonates are all suitable substrates for this transformation, delivering the desired branched products in high yields and optical purities. Heterocycles are tolerated as well. One exception for the generally high enantiocontrol under the Pd/MeO-Fur-BIPHEP catalysis is that when the coupling partners bearing strongly electron withdrawing groups are used, such as the one **3.53**, 1,5-dienes are formed in much lower enantiomeric purity (entry 5). We suspect that for one of substrates containing electron withdrawing groups, reductive elimination may be accelerated by the increased electronic difference between the two distal carbons, in a similar manner to that for bis(aryl)palladium;<sup>24</sup> this would render the transmetallation step stereochemistry-determining and may result in diminished enantioselectivity.

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<sup>24</sup> Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, 23, 3398.

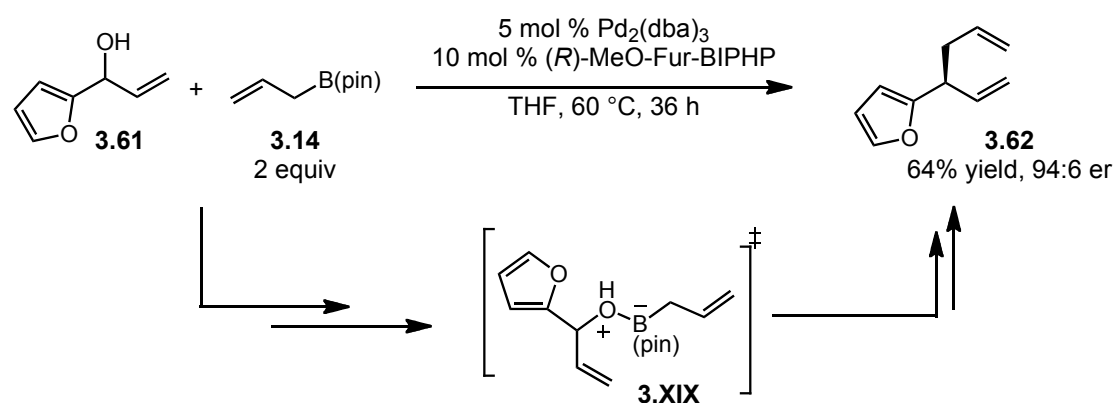
**Table 3.7 Substrates Bearing Aromatic Substituents**

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <math display="block">  \begin{array}{c}  \text{R}-\text{CH}=\text{CH}-\text{CH}_2-\text{OBoc} \\  \text{or} \\  \text{R}-\text{CH}(\text{OBoc})-\text{CH}=\text{CH}_2  \end{array}  + \text{CH}_2=\text{CH}-\text{CH}_2-\text{B}(\text{pin})  </math> <p><b>3.14</b> 1.2 equiv</p> </div> <div style="text-align: center;"> <math display="block">  \xrightarrow[\text{THF, 60 } ^\circ\text{C}]{\begin{array}{c} 5 \text{ mol } \% \text{ Pd}_2(\text{dba})_3 \\ 10 \text{ mol } \% \text{ ligand} \end{array}}  </math> </div> <div style="text-align: center;"> <math display="block">  \begin{array}{c}  \text{R}' \\    \\  \text{R}-\text{CH}_2-\text{CH}=\text{CH}_2  \end{array}  </math> </div> </div> <div style="margin-top: 10px; text-align: right;"> <div style="border: 1px solid black; padding: 5px; display: inline-block;">  <p><b>3.44</b> (R)-MeO-Fur-BIPHEP</p> </div> </div>				
entry	substrate	product	%yield	er
1	 <b>3.49</b>	 <b>3.16</b>	75	97:3
2	 <b>3.50</b>	 <b>3.16</b>	72	96:4
3 <sup>a</sup>	 <b>3.51</b>	 <b>3.56</b>	87	95:5
4	 <b>3.52</b>	 <b>3.57</b>	52	95:5
5	 <b>3.53</b>	 <b>3.58</b>	67	87:13
6	 <b>3.54</b>	 <b>3.59</b>	59	95:5
7	 <b>3.55</b>	 <b>3.60</b>	83	96:4

<sup>a</sup> 1.5 equiv of allylB(pin).

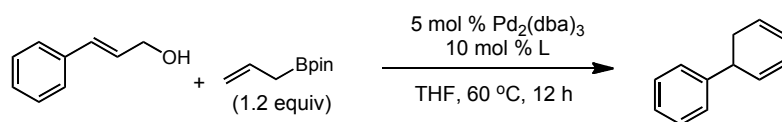
Remarkably, unactivated alcohols are also competent substrates in the allyl-allyl coupling. As demonstrated in Scheme 3.16, allylic alcohol **3.61** reacts smoothly under palladium catalysis, coupling with allylB(pin) in high efficiency and stereocontrol. We believe the reaction involves a Lewis acid-Lewis base interaction between boron and the alcohol moiety (likely through **3.XIX**), which activates the hydroxyl as a leaving group for Pd(0) addition and initiates the catalytic cycle. This feature currently appears to be most effective with electron-rich compounds, suggesting that additional electron resonance donation from substrates is necessary.<sup>25</sup>

**Scheme 3.16**



The scope of allyl-allyl coupling with alkyl-substituted carbonates is the given in Table 3.8. Employing QuinoxP\* as the ligand allows these transformations to proceed smoothly and stereoselectively. The regioselectivity generally is not as good as that

<sup>25</sup> Additional data for cinnamyl alcohol as substrate:



L	%conv.
dpp-benzene	21
QuinoxP*	<5
MeO-Fur-BIPHEP	<5

observed with aromatic substrates, but still is in a synthetically useful level. In addition to *n*-alkyl substrates (**3.63**), protected alcohol functionalities are well tolerated (**3.66** and **3.67**). The primary alcohol derived cyclohexyl substrate (**3.64**) exhibits extremely poor reactivity and regiocontrol, presumably caused by non-efficient coordination of the sterically hindered alkene to palladium center, which may slow down the oxidative addition. This problem is remedied by employing the branched analogue of this allylic carbonate, delivering the desired 1,5-diene in good yield and excellent optical purity (entry 3).

**Table 3.8 Aliphatic Substrates**

**3.35**  
(*R,R*)-QuinoxP\*

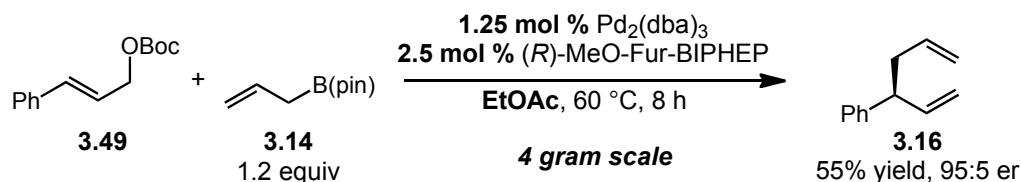
entry	substrate	product	%yield	b:l	er
1	<p><b>3.63</b></p>	<p><b>3.68</b></p>	80	10:1	92:8
2	<p><b>3.64</b></p>	<p><b>3.69</b></p>	9	3:1	97:3
3	<p><b>3.65</b></p>		63	10:1	96:4
4 <sup>a</sup>	<p><b>3.66</b></p>	<p><b>3.70</b></p>	91	>20:1	95:5
5	<p><b>3.67</b></p>	<p><b>3.71</b></p>	75	10:1	93:7

<sup>a</sup> 1.2 equiv Cs<sub>2</sub>CO<sub>3</sub> was used.

To probe the practical utility of Pd-catalyzed allyl-allyl cross-coupling, a representative 4-gram-scale reaction was carried out. It was found that the catalyst loading could be lowered to 2.5 mol % of palladium and THF, the typical solvent used in

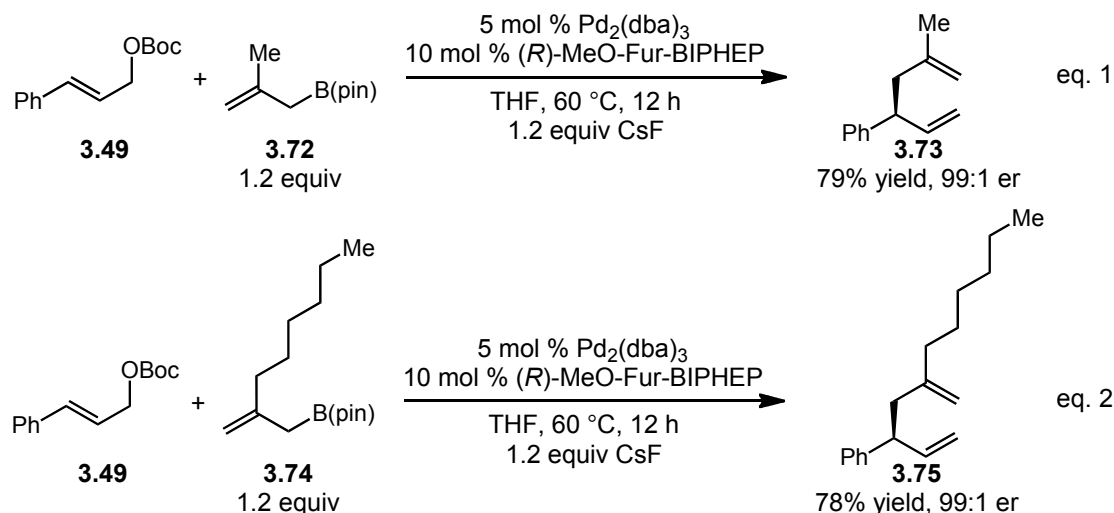
cross-coupling, could be replaced with environmentally more friendly EtOAc (Scheme 3.17). Under these conditions, the allyl-allyl coupling could be conducted on large scale and still delivered the branched 1,5-diene in relatively good yield and excellent enantioselectivity.

**Scheme 3.17**



Easily accessed  $\beta$ -substituted allylic boronates were also prepared and employed in the allyl-allyl coupling. Likely due to the  $\beta$ -substituents, reactivities of these reagents (**3.72** and **3.74**, Scheme 3.18) were found to be lower than non-substituted allylB(pin). These reactions were improved by employing CsF as an additive, presumably by accelerating transmetallation. As demonstrated in Scheme 3.18, both 2-methyl and 2-*n*-hexyl allylborates undergo the Pd-catalyzed cross-coupling smoothly and furnish products in exceptional enantiomeric purity.

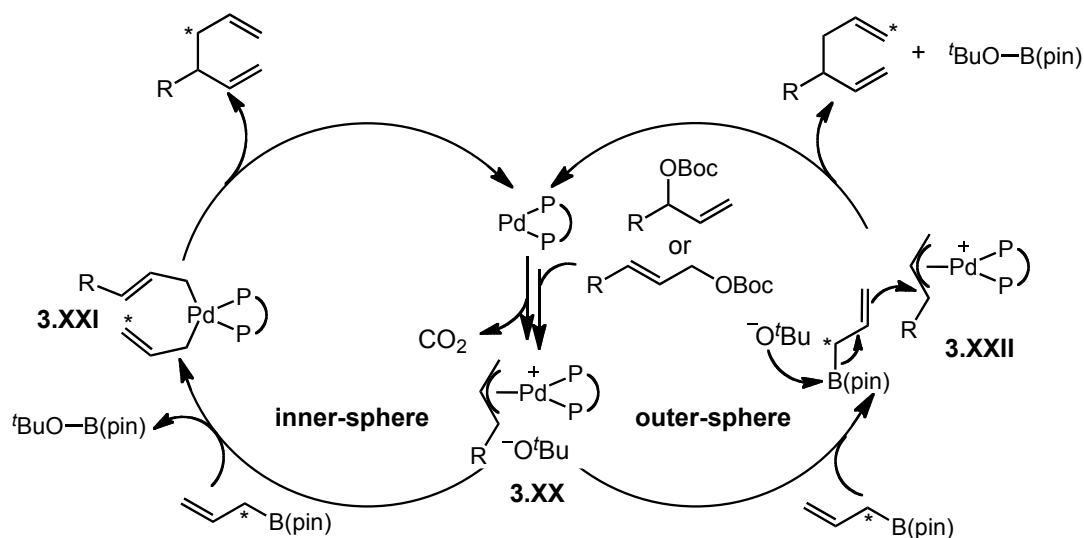
**Scheme 3.18**



**D. Mechanistic Proposal.** The observation that similar levels of enantioselectivity are obtained regardless of the isomeric forms of the starting materials suggests that common intermediates are generated during the catalytic cycle. It is well documented that oxidative addition of allylic carbonates to Pd(0) complexes yields  $\pi$ -allyl-palladium complexes (such as **3.XX**, in Scheme 3.19). Subsequent reaction with allylB(pin) may occur by transmetallation from base-activated boron to palladium. We hypothesize that the resulting bis( $\eta^1$ -allyl)palladium complex (**3.XXI**) reductively eliminates to afford the 1,5-diene product. When the initial  $\eta^3$ -allyl ligand on Pd adopts the  $\eta^1$  configuration allowing another allyl ligand to bind, the substituent is likely to move away from the metal center instead of forming a sterically hindered secondary carbon-palladium bond. Therefore, upon favorable 3,3'-reductive elimination, branched products are furnished.

Alternatively, the reaction may proceed through an outer-sphere pathway, wherein the  $\pi$ -allyl-palladium complex is attacked by activated allylB(pin) from the backside (as demonstrated in complex **3.XXII**) to directly form the carbon-carbon bonds. Similar mechanisms have been proposed for Pd-catalyzed allylations involving soft nucleophiles, and allylstannane,<sup>1,2</sup> allylsilane<sup>26</sup> and enolate nucleophiles.<sup>27</sup>

**Scheme 3.19**



**E. Preliminary Mechanistic Study.** To distinguish between the inner-sphere and outer-sphere mechanistic possibilities, the deuterium-labeled allylB(pin) (**3.75**) was employed as the coupling partner in the Pd-catalyzed allyl-allyl cross-coupling reaction. As described above, allylB(pin) is likely to transmetallate onto Pd or attack the  $\pi$ -allyl-Pd complexes in a  $\text{S}_{\text{E}}2'$  fashion, in the similar manner with allylsilanes and other allylmetal

<sup>26</sup> Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

<sup>27</sup> Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.

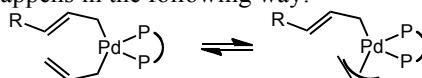


reagents.<sup>28</sup> We anticipated that upon the reaction, the deuterium label would be on the terminus of the 1,5-diene (**3.76**, Scheme 3.20) for the outer-sphere pathway whereas for the inner-sphere **3.77** will be formed (the deuterium-label is marked as \* in catalytic cycle, Scheme 3.19). It was beyond our expectations that, when the experiment was conducted with the presence of the chiral ligand, the deuterium label was found at both allyl termini in the reaction product. It may be expected that isotope scrambling would not occur in the outer-sphere pathway unless allylic isomerization of allylB(pin) proceeds rapidly under the reaction conditions. However, the unreacted allylB(pin) was confirmed to be isomerically pure, discounting this possibility. For the inner-sphere mechanism, equilibration of the bis(allyl)palladium complex (**3.XXI**, Scheme 3.19) might be expected and may account for the reaction outcome.<sup>29</sup> It is worth noting that to allow for such an isomerization to occur, five-coordinated  $(\eta^1\text{-allyl})(\eta^3\text{-allyl})(\text{diphosphine})\text{palladium}$  complex is presumably required. Though this complex is uncommon for Pd(II) species, such complexes are known and characterized, which supports the accessibility of the intermediates required for isotope scrambling.<sup>30</sup>

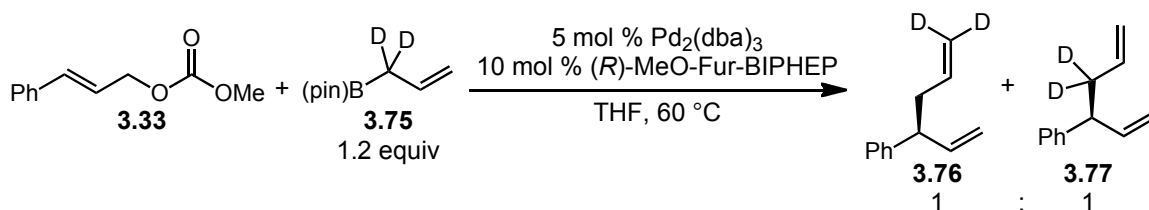
<sup>28</sup> For representative examples of allylsilanes transmetallating to Pd(II) through  $S_E2'$  path: (a) Hatanaka, V.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, 35, 1279. For representative examples of allylmetals react as nucleophiles in  $S_E2'$  fashion: (b) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, 103, 1969. (c) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, 104, 4963. (d) Hayashi, T.; Kabeta, K.; Yamamoto, T.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1983**, 24, 5661. (e) Wickham, G.; Kitching, W. *J. Org. Chem.* **1983**, 48, 614. (f) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, 2, 749.

<sup>29</sup> For representative examples of bis(allyl)palladium equilibration: (a) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, 130, 4978. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1983**, 736. (c) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Tetrahedron Lett.* **1989**, 45, 1067. (d) Hiyama, T.; Matsuhashi, H.; Fujita, A.; Tanaka, M.; Hirabayashi, K.; Shimizu, M.; Mori, A. *Organometallics* **1996**, 15, 5762.

<sup>30</sup> The isotope scrambling likely happens in the following way:

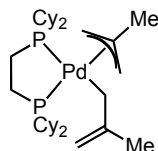


### Scheme 3.20

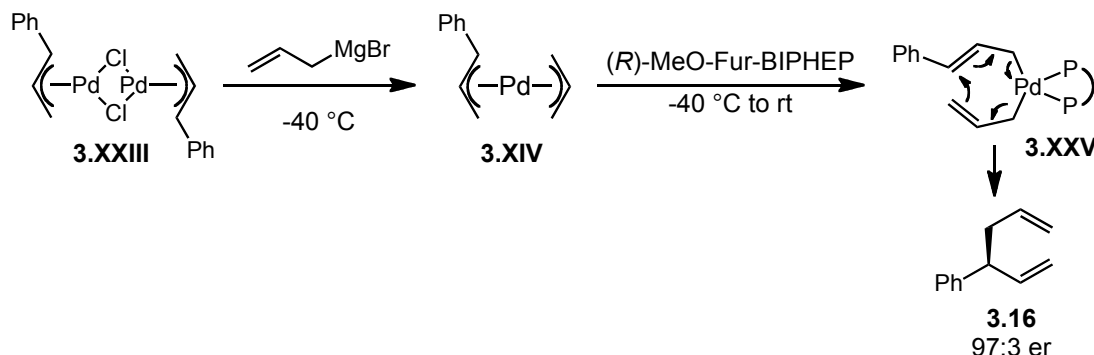


To further validate the proposed inner-sphere pathway, the stoichiometric reductive elimination of a (cinnamyl)(allyl)palladium(II) complex, inspired by Schwartz's work,<sup>6a-c</sup> was studied. The  $(\eta^3\text{-allyl})(\eta^3\text{-cinnamyl})$ palladium complex (**3.XIV**, Scheme 3.21) was synthesized and treated with  $(R)\text{-MeO-Fur-BIPEHP}$ . It was expected that upon bidentate ligand binding,  $(\eta^1\text{-allyl})(\eta^1\text{-cinnamyl})(\text{biphosphine})$ palladium (**3.XIV**) would be formed, followed by generation of the branched 1,5-diene through ligand induced reductive elimination. The enantioselectivity of this reaction should also be consistent with the corresponding catalytic reaction, when  $(R)\text{-MeO-Fur-BIPEHP}$  is employed. Although **3.16** was synthesized in 97:3 er through this path occasionally, this reaction suffered from lack of reproducibility. Unfortunately efforts to better control the reaction by manipulating the reaction conditions failed.

Similar 5-coordinated palladium complex has been synthesized and characterized: Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, 24, 283.



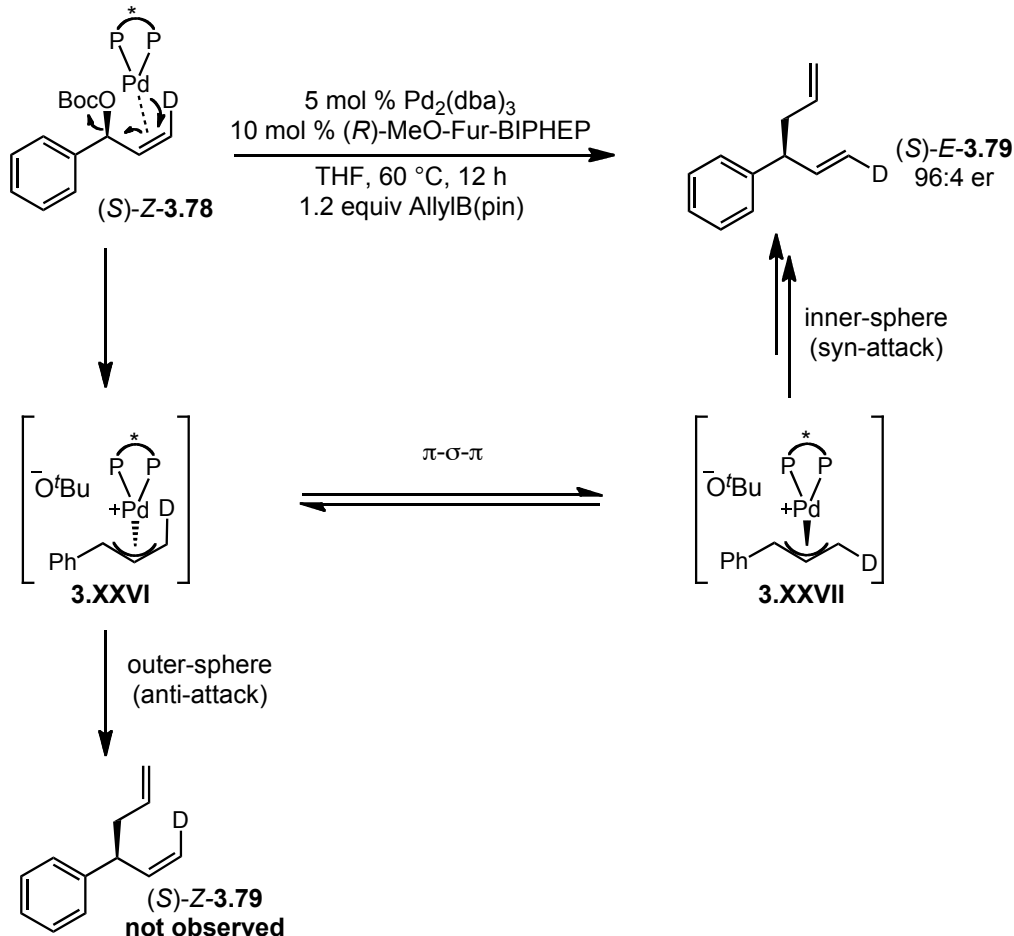
### Scheme 3.21



Another deuterium labeling experiment was designed to support the inner-sphere mechanism. Enantiomerically enriched (*S*)-**Z-3.78** was prepared and subjected to the enantioselective allyl-allyl cross-coupling with (*R*)-MeO-Fur-BIPEHP as the ligand. It has been shown that Pd(0) adds to the allylic carbonate electrophile through *anti* displacement.<sup>31</sup> Therefore,  $\pi$ -allyl-palladium complex (**3.XXVI**) would be formed as a single diastereomer. Subsequently, **3.XXVI** could directly deliver the observed enantiomer product through an outer-sphere attack by the allylic nucleophile, and the product would be the *Z* isomer. Alternatively, complex **3.XXVII**, derived from **3.XXVI** *via* the  $\pi$ - $\sigma$ - $\pi$  equilibration, would yield the *E* isomer by inner-sphere reductive elimination. The experiment yielded (*S*)-**E-3.79** as a single product in 96:4 er. This outcome is only consistent with the inner-sphere mechanism. (Scheme 3.22)

<sup>31</sup> (a) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

**Scheme 3.22**



#### IV. CONCLUSIONS

The first palladium-catalyzed, highly branch- and enantioselective allyl-allyl cross-coupling has been developed. The reaction is most effective when allylic carbonates are utilized as substrates, whereas acetates require external activation. The regiocontrol is found to rely on the bite angle of the biphosphine ligands, with small bite angle ligands favoring branch products. Two optimal chiral ligands have been identified, which promote the allyl-allyl coupling effectively and in high levels of enantiocontrol. A

good level of substitution is tolerated in this reaction, delivering 1,5-dienes bearing tertiary carbon centers in good yields and excellent optical purity. Preliminary mechanistic studies have suggested the 3,3'-reductive elimination of bis(allyl)(diphosphine)palladium(II) is responsible for the observed regioselection.

## V. EXPERIMENTAL PROCEDURES

### A. General Information

<sup>1</sup>H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz) or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl<sub>3</sub>: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), coupling constants (Hz), and assignment. <sup>13</sup>C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Gemini-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl<sub>3</sub>: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer,  $\nu_{\text{max}}$  cm<sup>-1</sup>. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

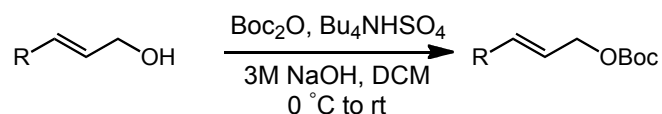
Liquid Chromatography was performed through the use of forced flow (flash chromatography) on silica gel (SiO<sub>2</sub>, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25  $\mu$ m silica gel plates purchased from

Silicycle. Visualization was performed through the use of ultraviolet light (254 nm) or potassium permanganate (KMnO<sub>4</sub>) in water. Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco  $\beta$ -Dex 120 column or a Supelco Chiraldex G-TA with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector with methanol as the modifier. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1120 compact chromatograph equipped with gradient pump and variable wavelength detector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter.

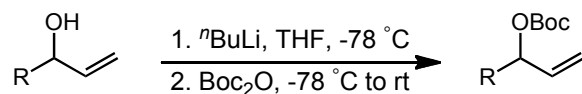
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) was purified through the use of a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Ethyl acetate was purified by drying with calcium hydride and distilled under N<sub>2</sub>. Tris(dibenzylideneacetone) dipalladium(0) [Pd<sub>2</sub>(dba)<sub>3</sub>], (R,R)-(-)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline [(R,R)-QuinoxP\*] and (R)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl [(R)-MeO-Fur-BIPHEP] as well as all the achiral bisphosphine ligands were purchased from Strem Chemicals, Inc. Allylboronic acid pinacol ester [allylB(pin)] was generously donated by Frontier Scientific, Inc. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

## B. Experimental Procedures

### 1. Preparation of Allylic Carbonates



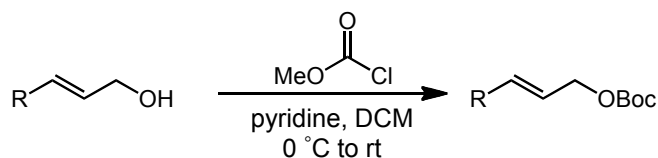
**Representative Procedure A:**<sup>32</sup> A round-bottomed flask with stir bar was charged with *p*-trifluoromethylcinnamyl alcohol (480 mg, 2.37 mmol) and methylene chloride (2 mL). To the resulting solution was added Boc<sub>2</sub>O (570 mg, 2.61 mmol) and Bu<sub>4</sub>NHSO<sub>4</sub> (16.0 mg, 0.047 mmol) at room temperature. The solution was cooled to 0 °C and aqueous NaOH (1.2 mL, 30% solution) was added dropwise. The solution was allowed to stir overnight. The reaction mixture was diluted with diethyl ether and water, and was then extracted into diethyl ether three times. The combined organics were washed with 1M HCl, water, then brine, and dried over MgSO<sub>4</sub>, filtered, then concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (22:1 hexanes: ethyl acetate) to afford 512 mg (72% yield) of a white solid. *R<sub>f</sub>* = 0.28 (22:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).



**Representative Procedure B:**<sup>32</sup> To a flame-dried round-bottomed flask with stir bar was added 1-(naphthalen-1-yl)prop-2-en-1-ol (530 mg, 2.88 mmol) and THF (7 mL). The solution was cooled to -78 °C (dry ice/acetone) and 1.18 mL (2.88 mmol) of a 2.45 M solution of butyllithium in hexane was added, dropwise. The solution was stirred for 30

<sup>32</sup> Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059.

minutes at -78 °C, Boc<sub>2</sub>O (629 mg, 2.88 mmol) in 4 mL THF was added. The reaction was allowed to warm to room temperature, stirring overnight. The reaction mixture was diluted with 10 mL of diethyl ether and 7 mL of water, and the mixture was stirred 15 minutes. The organic layer was separated and the aqueous layer was extracted into diethyl ether three times. Combined organics were washed with brine then dried over MgSO<sub>4</sub>, filtered, then concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (24:1 hexanes: ethyl acetate) to afford 691 mg (84%) of a clear, colorless oil. *R<sub>f</sub>* = 0.38 (20:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).



**Representative Procedure C:**<sup>33</sup> A flame-dried round-bottomed flask with stir bar was charged with (*E*)-dec-2-en-1-ol (1.56 g, 10.0 mmol), methylene chloride (20 mL) and pyridine (1.19 g, 15.0 mmol). The resulting solution was cooled to 0 °C (ice-water) and then methyl chloroformate (570 mg, 2.61 mmol) was added dropwise. The reaction was allowed to stir at this temperature for an hour and then warm up to room temperature for another 12 hours. At this time, water was added, and the organic layer was washed with methylene chloride three times. The combined organic layers were then washed with saturated CuSO<sub>4</sub>, followed by saturated NH<sub>4</sub>Cl and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, then concentrated. The crude reaction mixture was purified on silica gel (50:1 hexanes: ethyl

<sup>33</sup> Gnamm, C.; Frank, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 20, 3331.



acetate) to afford 2.10 g (99%) of a light yellow oil.  $R_f = 0.45$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

***Preparation of tert-butyl cinnamyl carbonate (3.49).*** From commercially available cinnamyl alcohol, procedure A was followed. Spectral data is in accordance with literature.<sup>32</sup>

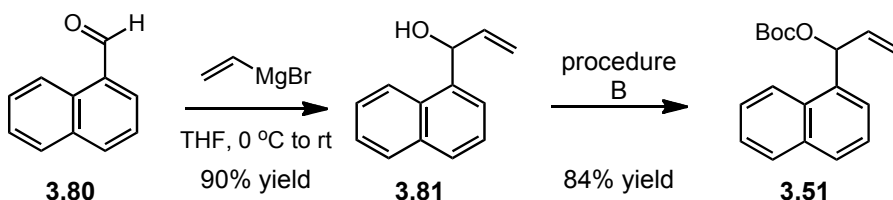
***Preparation of cinnamyl methyl carbonate (3.33).*** From commercially available cinnamyl alcohol, procedure C was followed. Spectral data is in accordance with literature.<sup>34</sup>

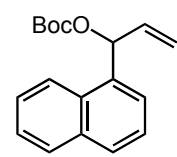
***Preparation of tert-butyl (1-phenylallyl) carbonate (3.50).*** From commercially available 1-phenylprop-2-en-ol, procedure B was followed. Spectral data is in accordance with literature.<sup>32</sup>

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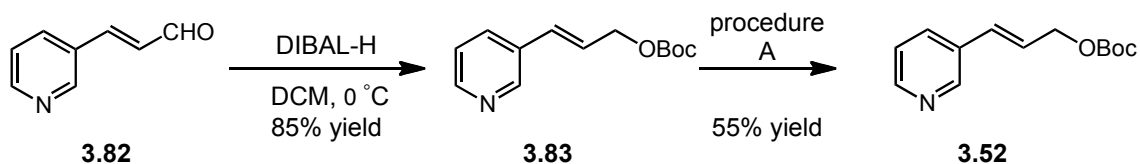
<sup>34</sup> Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.

**Preparation of *tert*-butyl (1-(naphthalen-1-yl)allyl) carbonate.** From allylic alcohol (**3.81**), synthesized as shown below, procedure B was followed.



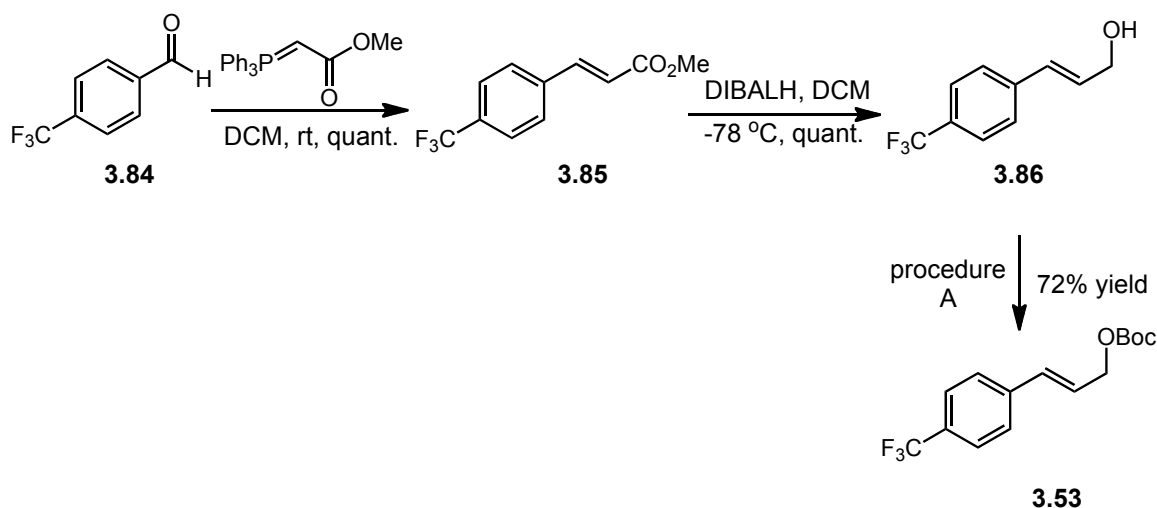
 ***tert*-butyl (1-(naphthalen-1-yl)allyl) carbonate (**3.51**).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.48 (9H, s,  $\text{OC}(\text{CH}_3)_3$ ), 5.30 (1H, app dt,  $J = 10.5$  Hz, 1.5 Hz,  $\text{COCH}=\text{CH}_{\text{cis}}$ ), 5.35 (1H, app dt,  $J = 17.0$  Hz, 1.5 Hz,  $\text{COCH}=\text{CH}_{\text{trans}}$ ), 6.21 (1H, ddd,  $J = 17.0$  Hz, 10.5 Hz, 5.5 Hz,  $\text{COCH}=\text{CH}_2$ ), 6.78 (1H, d,  $J = 5.5$  Hz, ArH), 7.46-7.56 (3H, m, ArH), 7.62 (1H, d,  $J = 7.0$  Hz, ArH), 7.83 (1H, d,  $J = 8.0$  Hz, ArH), 7.87 (1H, dd,  $J = 7.5$  Hz, 1.5 Hz, ArH), 8.12 (1H, d,  $J = 8.5$  Hz, ArH);  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  27.8, 76.3, 82.4, 117.5, 123.6, 125.1, 125.3, 125.7, 126.3, 128.8, 128.9, 130.6, 133.8, 134.4, 135.8, 152.9; IR (neat): 2980.0 (w), 1736.1 (s), 1368.6 (w), 1271.4 (s), 1250.1 (s), 1154.7 (s), 1101.1 (m), 1082.8 (m), 965.0 (m), 930.1 (m), 882.7 (m), 846.4 (m), 775.2 (s), 435.4 (w)  $\text{cm}^{-1}$ ; HRMS (TOF MS ES+) for  $\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}$  [ $\text{M}+\text{Na}$ ]: calculated: 307.1310, found: 307.1314; The crude reaction mixture was purified on silica gel (25:1 hexanes: ethyl acetate) to afford a clear, colorless oil (84% yield).  $R_f = 0.38$  (20:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

**Preparation of (*E*)-*tert*-butyl (3-(pyridin-3-yl)allyl) carbonate.** From allylic alcohol (3.83), synthesized as shown below, procedure A was followed.



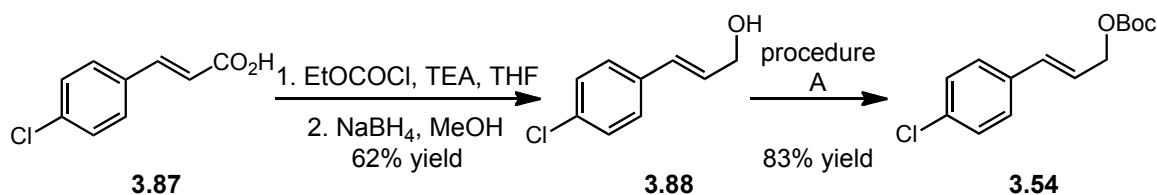
(*E*)-*tert*-butyl (3-(pyridin-3-yl)allyl) carbonate (3.52).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.44 (9H, s,  $\text{OC}(\text{CH}_3)_3$ ), 4.73 (2H, dd,  $J = 6.4$  Hz, 1.2 Hz,  $\text{CH}_2\text{OBoc}$ ), 6.36 (1H, dt,  $J = 16.0$  Hz, 6.0 Hz,  $\text{ArCH}=\text{CH}$ ), 6.65 (1H, d,  $J = 16.0$  Hz,  $\text{ArCH}=\text{CH}$ ), 7.23-7.26 (1H, m,  $\text{ArH}$ ), 7.69 (1H, app dt,  $J = 8.0$  Hz, 1.6 Hz,  $\text{ArH}$ ), 8.48 (1H, dd,  $J = 4.8$  Hz, 1.6 Hz,  $\text{ArH}$ ), 8.60 (1H, s,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  27.8, 66.9, 82.5, 123.4, 125.4, 130.4, 131.8, 133.0, 148.5, 149.1, 153.2; IR (neat): 1736.2 (s), 1369.1 (m), 1251.6 (s), 1157.4 (s), 1114.9 (m), 968.2 (m), 861.5 (m), 791.8 (m), 707.0 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{18}\text{NO}_3$   $[\text{M}+\text{H}]$ : calculated: 236.1287, found: 236.1290; The crude reaction mixture was purified on silica gel (4:1 hexanes: ethyl acetate with 2% triethylamine) to afford a clear, colorless oil (55% yield).  $R_f = 0.12$  (4:1 hexanes: ethyl acetate with 2% triethylamine, visualize by UV).

**Preparation of (*E*)-*tert*-butyl(3-(4-(trifluoromethyl)phenyl)allyl) carbonate.** From allylic alcohol (**3.86**), synthesized as shown below, procedure A was followed.



**(*E*)-*tert*-butyl(3-(4-(trifluoromethyl)phenyl)allyl) carbonate**  
**(3.53).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.51 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 4.74 (2H, dd, *J* = 6.4 Hz, 1.6 Hz, CH<sub>2</sub>OBoc), 6.38 (1H, dt, *J* = 16.0 Hz, 6.0 Hz, ArCH=CH), 6.70 (1H, d, *J* = 16.0 Hz, ArCH=CH), 7.48 (2H, d, *J* = 8.4 Hz, ArH), 7.58 (2H, d, *J* = 8.0 Hz, ArH); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 27.8, 66.9, 82.5, 125.6 (q, *J* = 3.7 Hz) 125.7, 126.8, 129.7, 130.0, 132.5, 139.7, 153.3; IR (neat): 2981.7 (w), 1738.3, (s), 1615.8 (w), 1370.0 (w), 1323.7 (s), 1272.0 (s), 1251.8, (s), 1156.5 (s), 1117.7 (s), 1066.3 (s), 968.5 (m), 953.1 (m), 930.9 (w), 852.6 (m), 791.8 (m), 756.1 (w), 597.9 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>10</sub>H<sub>8</sub>F<sub>3</sub> [M-OBoc]: calculated: 185.0573, found: 185.0579; The crude reaction mixture was purified on silica gel (22:1 hexanes: ethyl acetate) to afford a white solid (72% yield). *R<sub>f</sub>* = 0.28 (22:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

**Preparation of (*E*)-*tert*-butyl (3-(4-chlorophenyl)allyl) carbonate.** From allylic alcohol (3.81), synthesized as shown below,<sup>35</sup> procedure A was followed.

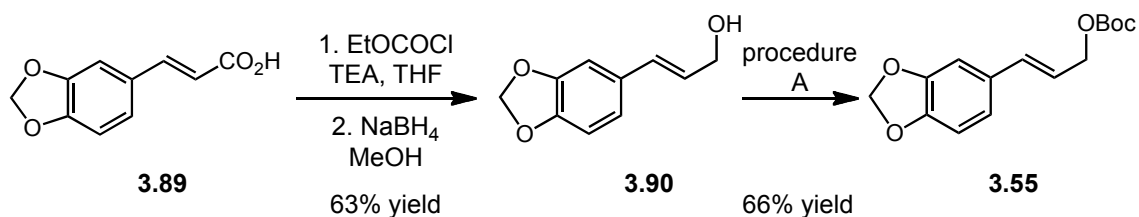


(*E*)-*tert*-butyl (3-(4-chlorophenyl)allyl) carbonate (3.54).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.50 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 4.71 (2H, dd, *J* = 6.5 Hz, 1.5 Hz, CH<sub>2</sub>OBoc), 6.27 (1H, dt, *J* = 16.0 Hz, 6.5 Hz, ArCH=CH), 6.62 (1H, d, *J* = 16.0 Hz, ArCH=CH), 7.28-7.32 (4H, m, ArH); <sup>13</sup>C NMR (125 Hz, CDCl<sub>3</sub>): δ 27.8, 67.2, 82.3, 123.7, 127.8, 128.8, 133.0, 133.8, 134.7, 153.3; IR (neat): 2980.9 (w), 1738.6 (s), 1491.6 (w), 1369.6 (m), 1252.8 (s), 1158.4 (s), 1117.2 (m), 1089.6 (m), 967.5 (w), 846.7 (m), 792.0 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>9</sub>H<sub>8</sub>Cl [M-OBoc]: calculated: 151.0309, found: 151.0317; The crude reaction mixture was purified on silica gel (20:1 hexanes: ethyl acetate) to afford a clear, colorless oil (83% yield). *R<sub>f</sub>* = 0.30 (20:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

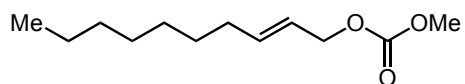
<sup>35</sup> Penjšević, J.; Šukalović, V.; Andrić, D.; Kostić-Rajačić, S.; Šoškic, V.; Roglić, G. *Arch. Pharm. Chem. Life. Sci.* **2007**, 340, 456.

**Preparation of (*E*)-3-(benzo[d][1,3]dioxol-5-yl)allyl tert-butyl carbonate.** From allylic alcohol (**3.55**), synthesized as shown below,<sup>35</sup> procedure A was followed.



(*E*)-3-(benzo[d][1,3]dioxol-5-yl)allyl tert-butyl carbonate (**3.55**). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.50 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 4.68 (2H, dd, *J* = 6.5 Hz, 1.5 Hz, CH<sub>2</sub>OBoc), 5.96 (2H, s, OCH<sub>2</sub>O), 6.12 (1H, dt, *J* = 15.5 Hz, 6.5 Hz, ArCH=CH), 6.57 (1H, d, *J* = 15.5 Hz, ArCH=CH), 6.75 (1H, d, *J* = 8.0 Hz, ArH), 6.82 (1H, dd, *J* = 8.0 Hz, 1.5 Hz, ArH), 6.92 (1H, d, *J* = 1.5 Hz, ArH); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 27.8, 67.5, 82.2, 101.1, 105.8, 108.3, 121.0, 121.5, 130.6, 134.3, 147.6, 148.0, 153.3; IR (neat): 2979.3 (w), 1734.7 (s), 1490.1 (m), 1445.0 (m), 1368.6 (m), 1271.7 (s), 1245.5 (s), 1155.5 (s), 1124.0 (w), 1036.2 (s), 963.0 (m), 925.8 (m), 855.1 (s), 792.2 (m), 611.5 (w), 418.3 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>10</sub>H<sub>9</sub>O<sub>2</sub> [M-OBoc]: calculated: 161.0597, found: 161.0604; The crude reaction mixture was purified on silica gel (20:1 hexanes: ethyl acetate) to afford a colorless oil (66% yield). *R<sub>f</sub>* = 0.12 (20:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

**Preparation of (*E*)-dec-2-enyl methyl carbonate.** From commercially available *trans*-2-decen-1-ol, procedure C was followed.



**(*E*)-dec-2-enyl methyl carbonate (3.63).**  $^1\text{H}$

NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.86 (3H, t,  $J = 6.8$  Hz,

$\text{CH}_2\text{CH}_3$ ), 1.25-1.39 (10H, m,  $\text{CH}_3(\text{CH}_2)_5$ ), 2.03 (2H, q,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ),

3.75 (3H, s,  $\text{OCH}_3$ ), 4.54 (2H, dd,  $J = 6.8, 0.8$  Hz,  $\text{CH}=\text{CHCH}_2\text{O}$ ), 5.55 (1H, dt,  $J = 15.6,$

6.4, 1.2 Hz,  $\text{CH}=\text{CHCH}_2\text{O}$ ), 5.79 (1H, dt,  $J = 15.6, 7.8$  Hz,  $\text{CH}=\text{CHCH}_2\text{O}$ );  $^{13}\text{C}$  NMR

(100 Hz,  $\text{CDCl}_3$ ):  $\delta$  14.0, 22.6, 28.7, 29.02, 29.04, 31.7, 32.2, 54.5, 68.6, 123.1, 137.5,

155.6; IR (neat): 2955.9 (w), 2925.4 (m), 2855.0 (w), 1747.2 (s), 1441.6 (m), 1379.7 (w),

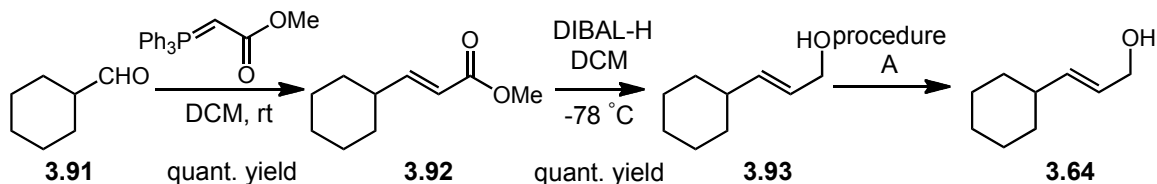
1252.5 (s), 943.0 (s), 792.0 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{19}$  [ $\text{M}-\text{OCO}_2\text{Me}$ ]: calculated:

137.1487, found: 139.1484; The crude reaction mixture was purified on silica gel (50:1

hexanes: ethyl acetate) to afford a clear, light yellow oil (99% yield).  $R_f = 0.45$  (8:1

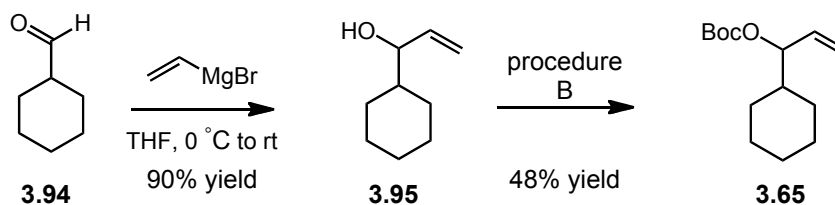
hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ )

**Preparation of (*E*)-*tert*-butyl (3-cyclohexylallyl) carbonate. (3.64).** From allylic alcohol (3.93), synthesized as shown below, procedure A was followed. Spectral data is in accordance with the literature.<sup>36</sup>



<sup>36</sup> Weix, D.J.; Markovi, D.; Ueda, M.; Hartwig, J. F. *Org. Lett.* **2009**, *11*, 2944.

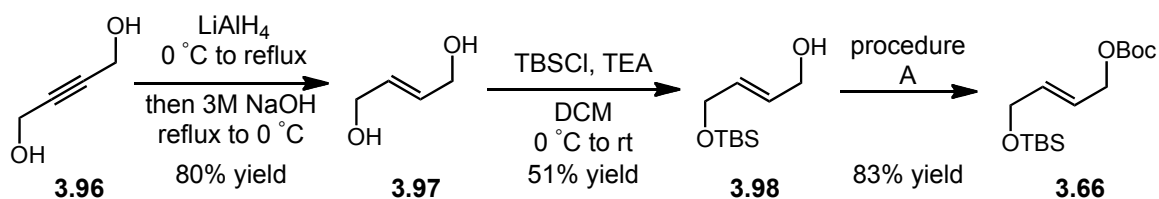
**Preparation of *tert*-butyl (1-cyclohexylallyl) carbonate.** From allylic alcohol (**3.95**), synthesized as shown below, procedure B was followed.



***tert*-butyl (1-cyclohexylallyl) carbonate (**3.65**).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.88-1.30 (6H, m, Cy-H), 1.46 (9H, m,  $\text{OC}(\text{CH}_3)_3$ ), 1.46-1.80 (5H, m, Cy-H), 4.67 (1H, app t,  $J = 7.2$  Hz, CyCHO), 5.19 (1H, dt,  $J = 10.4, 1.2$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}$ ), 5.22 (1H, dt,  $J = 17.2, 1.2$  Hz,  $\text{CH}=\text{CH}_{\text{trans}}$ ), 5.75 (1H, ddd,  $J = 17.2, 10.4, 7.2$  Hz,  $\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  25.8, 25.9, 26.3, 27.8, 28.4, 28.5, 41.5, 81.6, 82.2, 117.7, 135.0, 153.2; IR (neat): 2980.5 (w), 2927.2 (m), 2854.3 (w), 1737.2 (s), 1451.4 (w), 1368.2 (w), 1272.7 (s), 1250.6 (s), 1160.9 (s), 958.3 (m), 855.0 (m), 792.1 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_9\text{H}_{15}$  [M-OBoc]: calculated: 123.1174, found: 123.1169; The crude reaction mixture was purified on silica gel (50:1 hexanes: ethyl acetate) to afford a clear, light yellow oil (48% yield).  $R_f = 0.52$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

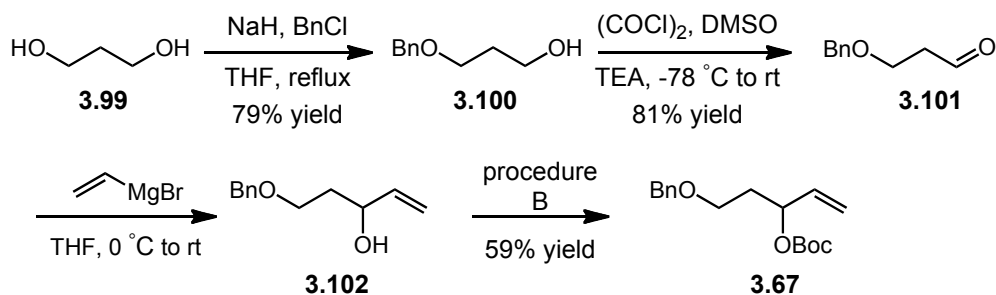


**Preparation of (*E*)-*tert*-butyl 4-(*tert*-butyldimethylsilyloxy)but-2-enyl carbonate.** From allylic alcohol (**3.98**), synthesized as shown below, procedure A was followed.



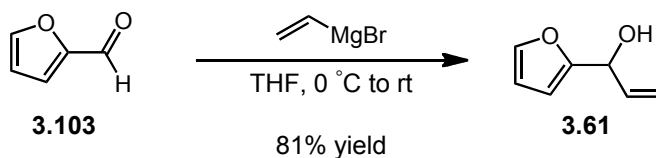
**(*E*)-*tert*-butyl 4-(*tert*-butyldimethylsilyloxy)but-2-enyl carbonate (**3.66**).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.03 (6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.87 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.45 (9H, s,  $\text{OC}(\text{CH}_3)_3$ ), 4.14-4.16 (2H, m,  $\text{SiOCH}_2\text{CH}=\text{CH}$ ), 4.52 (2H, d,  $J = 4.8$  Hz,  $\text{CH}=\text{CHCH}_2\text{OBoc}$ ), 5.75-5.87 (2H, m,  $\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  -5.4, 18.3, 25.8, 27.7, 62.7, 66.8, 81.9, 123.2, 134.4, 153.3; IR (neat): 2954.8 (w), 2930.6 (w), 2886.3 (w), 2857.0 (w), 1740.1 (s), 1462.0 (w), 1391.7 (w), 1368.6 (m), 1274.2 (s), 1161.9 (s), 1106.7 (s), 1050.4 (m), 833.6 (s), 774.7 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{21}\text{OSi}$  [M-OBoc]: calculated: 185.1362, found: 185.1363; The crude reaction mixture was purified on silica gel (35:1 hexanes: ethyl acetate) to afford a clear, light yellow oil (83% yield).  $R_f = 0.41$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

**Preparation of 5-(benzyloxy)pent-1-en-3-yl tert-butyl carbonate.** From allylic alcohol (3.102), synthesized as shown below, procedure B was followed.

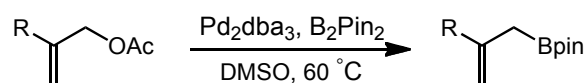


**5-(benzyloxy)pent-1-en-3-yl tert-butyl carbonate (3.67).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.48 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 1.86-1.94 (1H, m, BnOCH<sub>2</sub>CH<sub>A</sub>), 1.98-2.07 (1H, m, BnOCH<sub>2</sub>CH<sub>B</sub>), 3.49-3.58 (2H, m, BnOCH<sub>2</sub>), 4.49 (2H, d, *J* = 0.8 Hz, PhCH<sub>2</sub>O), 5.18-5.24 (1H, m, CHOBoc), 5.19 (1H, app dt, *J* = 10.4 Hz, 1.2 Hz, COCH=CH<sub>cis</sub>), 5.29 (1H, app dt, *J* = 17.2 Hz, 1.2 Hz, COCH=CH<sub>trans</sub>), 5.81 (1H, ddd, *J* = 17.2 Hz, 10.4 Hz, 6.8 Hz, COCH=CH<sub>2</sub>), 7.26-7.35 (5H, m, PhH); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 27.8, 34.5, 66.1, 73.1, 75.2, 82.0, 117.2, 127.6, 127.7, 128.4, 136.1, 138.3, 152.8; IR (neat): 2979.5 (w), 2931.1 (w), 2863.0 (w), 1738.5 (s), 1455.0 (w), 1368.4 (m), 1273.5 (s), 1253.6 (s), 1161.2 (s), 1100.8 (s), 990.0 (w), 931.3 (m), 854.1 (m), 792.3 (w), 737.7 (m), 697.9 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>17</sub>H<sub>24</sub>O<sub>4</sub> [M+H]<sup>+</sup>: calculated: 293.1753, found: 293.1751; The crude reaction mixture was purified on silica gel (100:1 hexanes: ethyl acetate) to afford a clear, colorless oil (59% yield). *R*<sub>f</sub> = 0.48 (8:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

**2. Preparation of 1-(furan-2-yl)prop-2-en-1-ol (3.61).** The allylic alcohol was synthesized as shown below. Spectral data is in accordance with the literature.<sup>37</sup>



**3. Representative Procedure for the Synthesis of  $\beta$ -Substituted AllylB(pin):**<sup>15a</sup>

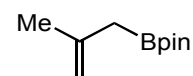


A flame dried round-bottomed flask with stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (69.0 mg, 0.075 mmol) and  $\text{B}_2(\text{pin})_2$  (1.70 g, 6.60 mmol) in a dry-box under an argon atmosphere. The flask was sealed with a septum, and removed from the dry-box. Under an atmosphere of nitrogen, freshly distilled DMSO (18 mL) was added by syringe, followed by methallyl acetate (342 mg, 3.00 mmol). The reaction mixture was then heated to 60 °C in an oil bath for 12 hours. The reaction was diluted with diethyl ether and brine, and the aqueous layer was washed with diethyl ether three times. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude reaction mixture was purified on silica gel (30:1 pentane: diethyl

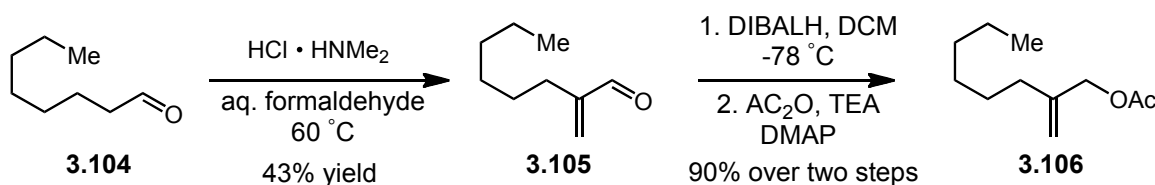
<sup>37</sup> Krauss, J.; Unterreitmeier, D. *Arch. Pharm. Chem. Life. Sci.* **2005**, 338, 44.

ether) to afford 338 mg (62% yield) of a clear, colorless oil.  $R_f = 0.35$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

**Preparation of 4,4,5,5-tetramethyl-2-(2-methallyl)-1,3,2-dioxaborolane.** From commercially available methallyl acetate.

 **4,4,5,5-tetramethyl-2-(2-methallyl)-1,3,2-dioxaborolane (3.72).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (12H, s,  $(\text{C}(\text{CH}_3)_2)_2$ ), 1.73 (2H, s,  $\text{BC}\text{H}_2$ ), 1.77 (3H, m,  $\text{CH}_2=\text{CCH}_3$ ), 4.66 (1H, m,  $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$ ), 4.68 (1H, m,  $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ): 24.5, 24.6, 24.7, 83.3, 110.2, 142.9; IR (neat): 3414.2 (br), 2978.8 (m), 2929.3 (w), 1647.6, (w), 1475.2 (m), 1455.2 (m), 1372.3 (s), 1325.6 (s), 1272.3 (m), 1143.8, (s), 982.1 (m), 881.4 (m), 849.5 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{20}\text{BO}_2$   $[\text{M}+\text{H}]$ : calculated: 183.1556, found: 183.1558; The crude reaction mixture was purified on silica gel (50:1 pentane: ether) to afford 336 mg of a clear, colorless oil (62% yield).  $R_f = 0.35$  (30:1 pentane: ether, stain in  $\text{KMnO}_4$ ).

**Preparation of 4,4,5,5-tetramethyl-2-(2-methyleneoctyl)-1,3,2-dioxaborolane.** From 2-methyleneoctyl acetate (**3.106**), synthesized as shown below.



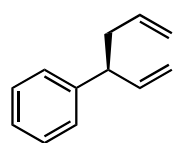
**4,4,5,5-tetramethyl-2-(2-methyleneoctyl)-1,3,2-dioxaborolane (**3.74**).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.23 (3H, t,  $J = 8.4$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.24 (12H, s,  $(\text{C}(\text{CH}_3)_2)_2$ ), 1.24-1.31 (6H, m,  $\text{CH}_3(\text{CH}_2)_3$ ), 1.40-1.55 (2H, m,  $\text{CH}_2\text{CH}_2\text{C}=\text{CH}_2$ ), 1.71 (2H, s,  $\text{CH}_2\text{B}(\text{pin})$ ), 2.04 (2H, t,  $J = 7.6$  Hz,  $\text{CH}_2\text{C}=\text{CH}_2$ ), 4.69 (1H, m,  $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$ ), 4.70 (1H, m,  $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  14.1, 22.6, 24.7, 27.6, 29.1, 31.8, 38.1, 83.2, 109.1, 146.8; IR (neat): 3072.7 (w), 2978.7 (m), 2957.2(m), 2927.7 (s), 2857.5 (m), 1743.9 (w), 1641.4 (w), 1466.8 (w), 1378.6 (m), 1325.2 (s), 1272.9 (w), 1144.4 (s), 878.4 (m), 848.4 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{30}\text{BO}_2$  [ $\text{M}+\text{H}$ ]: calculated: 253.2339, found: 253.2341; The crude reaction mixture was purified on silica gel (100:1 pentane: diethyl ether) to afford a clear, colorless oil (11% yield).  $R_f = 0.44$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

#### 4. Representative Procedure for Pd-Catalyzed Allyl-Allyl Cross-Coupling:

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (4.6 mg, 0.005 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (5.4 mg, 0.010 mmol), and 0.20 mL of

THF in a dry-box under an argon atmosphere. The vial was capped and stirred for 5 minutes, then *tert*-butyl cinnamyl carbonate (23.4 mg, 0.100mmol) was added, followed by allylboronic acid pinacol ester (20.1 mg, 0.120 mmol). The vial was sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. After this time period, the reaction vial was cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of silica gel and concentrated *in vacuo*. Analysis of the crude reaction mixture through the use of <sup>1</sup>H NMR was used to determine the branched to linear product ratio. Silica gel chromatography (pentane) afforded 11.4 mg (72%) of a colorless oil of the allyl-allyl coupling product as a mixture of isomers.

## 5. Characterization and Proof of Stereochemistry

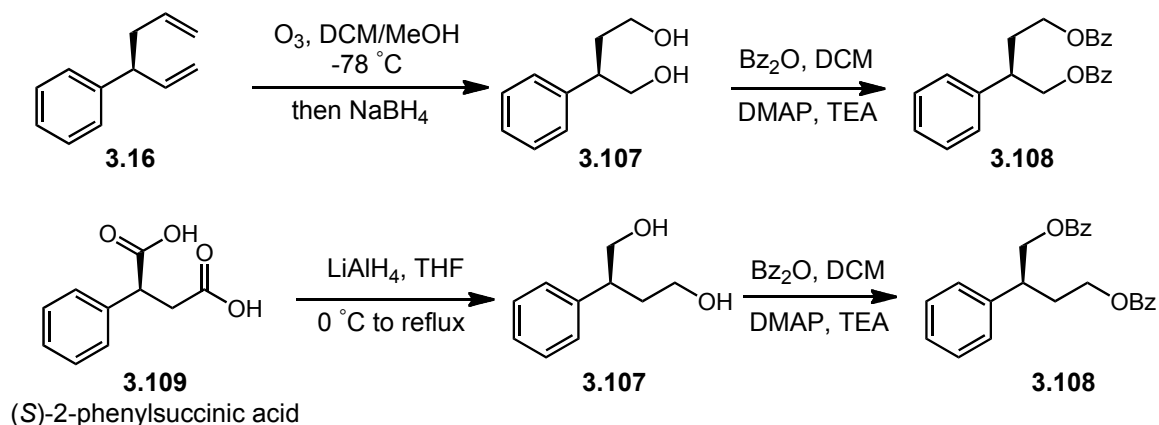


**(S)-hexa-1,5-dien-3-ylbenzene (3.16).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 2.47-2.51 (2H, m, CHCH<sub>2</sub>CH=CH<sub>2</sub>), 3.36 (1H, app q, *J* = 7.5 Hz, CHCH<sub>2</sub>CH=CH<sub>2</sub>), 4.96-5.07 (4H, m, CHCH=CH<sub>2</sub> & CH<sub>2</sub>CH=CH<sub>2</sub>), 5.73 (1H, ddt, *J* = 17.0 Hz, 10.0 Hz, 7.5 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.98 (1H, ddd, *J* = 17.0 Hz, 10.0 Hz, 7.5 Hz, CHCH=CH<sub>2</sub>), 7.19-7.22 (3H, m, PhH), 7.29-7.32 (2H, m, PhH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 39.7, 49.6, 114.4, 116.1, 126.3, 127.7, 128.4, 136.6, 141.6, 143.7; IR (neat): 3078.0 (w), 3028.0 (w), 3003.9 (w), 2977.9 (w), 2924.3 (w), 1631.0 (s), 1601.2 (w), 1492.2 (s), 1452.0 (s), 1415.0 (w), 1073.2 (w), 991.4 (m), 910.2 (s), 753.1 (m), 697.6 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>12</sub>H<sub>15</sub> [M+H]<sup>+</sup>: calculated: 159.1174, found: 159.1176; [α]<sub>D</sub><sup>20</sup> =

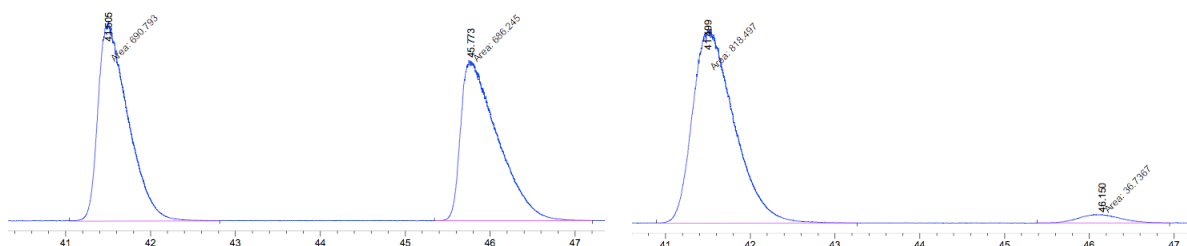
+12.237 ( $c = 0.44$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (11.4 mg, 72% yield).  $R_f = 0.38$  (pentane, stain in  $\text{KMnO}_4$ ).

***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by converting the allyl-allyl coupling product to a dibenzoate by ozonolysis/reduction and benzoate protection of the corresponding diol, as shown below. *Via* chiral HPLC, the resulting dibenzoate (**3.108**) was compared to authentic (*S*)-2-phenylbutane-1,4-diyl dibenzoate, which was derived from commercially available (*S*)-2-phenylsuccinic acid.



*Chiral GLC (CD-GTA, Supelco, 60 °C, 25 psi) - analysis of title compound.*

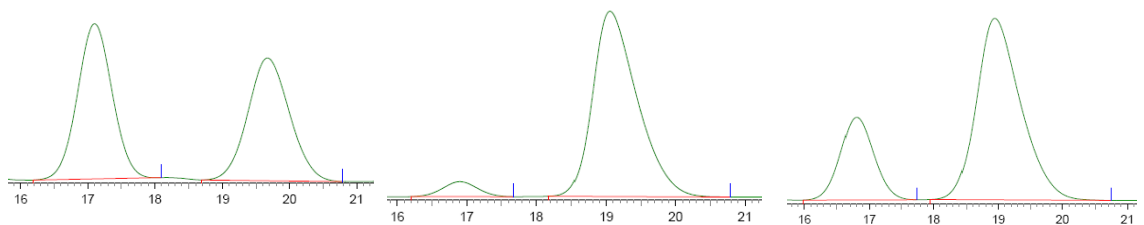


racemic

reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	41.499	MM	0.5666	818.49750	24.07773	95.70448
2	46.150	MM	0.5839	36.73672	1.04862	4.29552

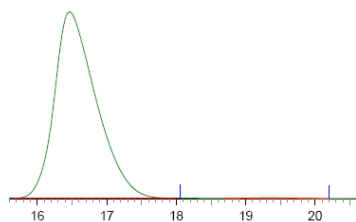
*Chiral HPLC (OD-R, Chiralcel, 1 mL/min, 1% isopropanol, 254 nm) – analysis of 2-phenylbutane-1,4-diyl dibenzoate.*



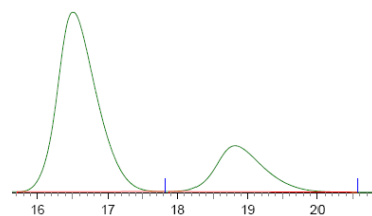
racemic

derived from reaction product

derivative + racemic



(S)-2-phenylbutane-1,4-diyl dibenzoate



(S)-2-phenylbutane-1,4-diyl dibenzoate

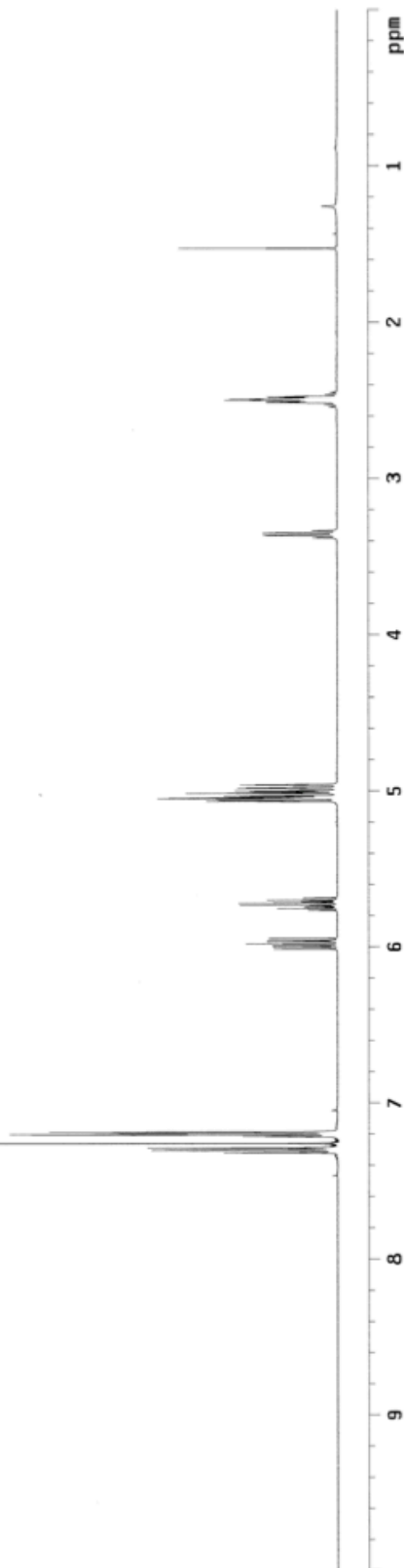
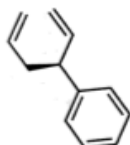
+ racemic




P2-433A-P

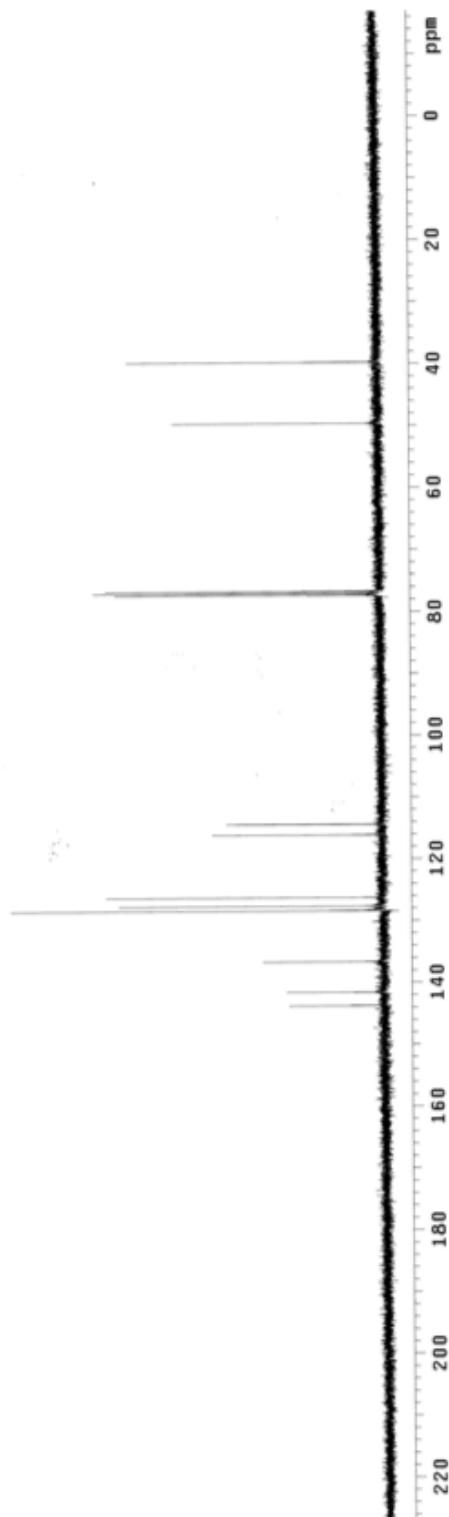
expl Proton

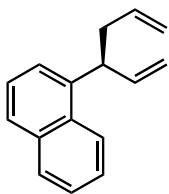
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fb	4	dp	y
bs	2	hs	nn
ss	1.000	fn	65536
di	16	fn	65536
nt	16	fn	65536
ct	16	fn	65536
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sfrq	495.888	wp	4998.7
tof	499.9	rfl	4842.4
tpwr	61	rfl	3829.2
pw	3.000	lp	114.8
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alif4	h1	h96	10.000
alif4	h1	h97	10.000
alif4	h1	h98	10.000
alif4	h1	h99	





**(S)-1-(hexa-1,5-dien-3-yl)naphthalene (3.56).**  $^1\text{H}$  NMR (500 MHz,

$\text{CDCl}_3$ ):  $\delta$  2.66-2.69 (2H, m,  $\text{ArCHCH}_2\text{CH}=\text{CH}_2$ ), 4.23 (1H, app q,  $J =$

7.0 Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 4.99-5.14 (4H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  &

$\text{ArCHCH}=\text{CH}_2$ ), 5.83 (1H, app ddt,  $J = 17.0$  Hz, 10.0 Hz, 7.0 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.12

(1H, ddd,  $J = 17.0$ , 10.5, 7.0 Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 7.40 (1H, d,  $J = 7.0$  Hz,  $\text{ArH}$ ), 7.44-

7.54 (3H, m,  $\text{ArH}$ ), 7.74 (1H, d,  $J = 8.0$  Hz,  $\text{ArH}$ ), 7.87 (1H, dd,  $J = 7.0$  Hz, 0.5 Hz,  $\text{ArH}$ ),

8.12 (1H, d,  $J = 8.0$  Hz,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  39.3, 43.9, 115.0, 116.2,

123.4, 124.2, 125.4, 125.5, 125.8, 126.9, 128.9, 131.6, 134.0, 136.8, 139.7, 141.1; IR

(neat): 3090.1 (w), 1638.2 (w), 992.1 (w), 911.9 (m), 796.3 (w), 776.4 (s)  $\text{cm}^{-1}$ ; HRMS

(ESI+) for  $\text{C}_{16}\text{H}_{17}$   $[\text{M}+\text{H}]$ : calculated: 209.1330, found: 209.1334;  $[\alpha]_D^{20} = +26.602$  ( $c =$

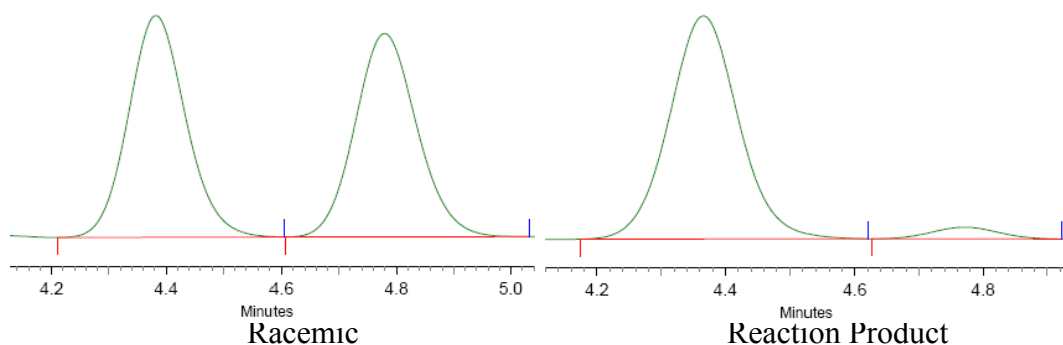
0.89,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a

clear, colorless oil (27.1 mg, 87% yield).  $R_f = 0.29$  (pentane, stain in  $\text{KMnO}_4$ ).

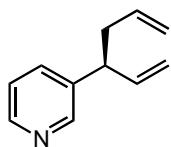
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

Chiral HPLC (OD-R, Chiraldex, 1 mL/min, 1% isopropanol in hexanes, 254 nm) – analysis of the title compound.



Retention Time	Area	Area %	Height	Height %
4.367	188084170	95.24	24956068	95.03
4.770	9408939	4.76	1303835	4.97



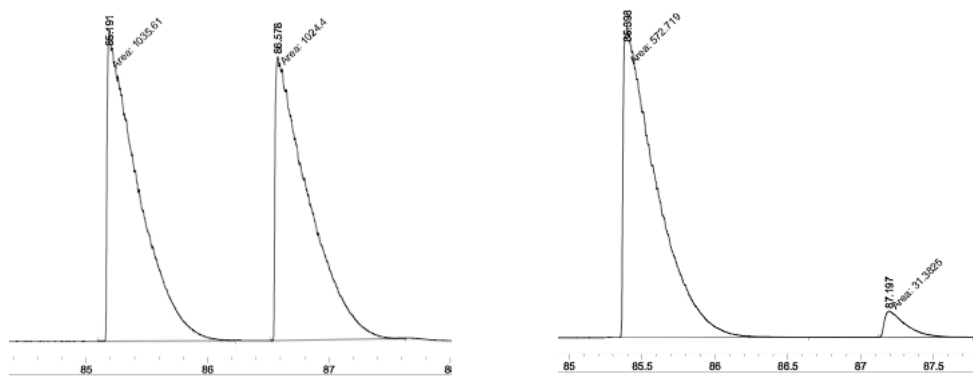
**(S)-3-(hexa-1,5-dien-3-yl)pyridine (3.57).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.44-2.57 (2H, m,  $\text{ArCHCH}_2\text{CH}=\text{CH}_2$ ), 3.40 (1H, app q,  $J = 7.0$  Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 4.98-5.01 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.05 (1H, app dt,  $J = 17.0$  Hz, 1.0 Hz,  $\text{ArCHCH}=\text{CH}_{\text{trans}}\text{H}$ ), 5.11 (1H, app dt,  $J = 10.5$  Hz, 1.0 Hz,  $\text{ArCHCH}=\text{CH}_{\text{cis}}\text{H}$ ), 5.70 (1H, app ddt,  $J = 17.5$  Hz, 10.5 Hz, 7.0 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.97 (1H, ddd,  $J = 17.0$  Hz, 10.5 Hz, 7.0 Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 7.23 (2H, m,  $\text{ArH}$ ), 7.50 (1H, app dt,  $J = 8.0$  Hz, 2.0 Hz,  $\text{ArH}$ ), 8.46 (1H, s,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  39.5, 46.9, 115.4, 116.9, 123.3, 135.1, 135.7, 138.8, 140.4, 147.8, 149.7; IR (neat): 3078.9 (w), 2925.5 (w), 1640.0 (w), 1574.5 (w), 1478.3 (w), 1423.6 (m), 1025.2 (w), 993.1 (m), 914.9 (s), 810.6 (w), 715.7 (s), 401.4 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{11}\text{H}_{14}\text{N}$   $[\text{M}+\text{H}]^+$ : calculated: 160.1126, found: 160.1119;  $[\alpha]_D^{20} = +21.938$  ( $c = 0.550$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel pretreated with 2% triethylamine in column eluent (3:1

pentane:diethyl ether) to afford a clear, light yellow oil (12.5 mg, 52% yield).  $R_f = 0.17$  (3:1 pentane:diethyl ether, visualize by UV).

***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

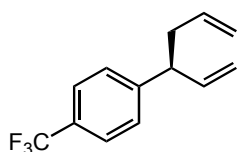
*Chiral GLC (CD-GTA, Supelco, 60 °C for 60 min, ramp 2 °C/min to 100 °C, 25 psi) – analysis of the title compound.*



Racemic

Reaction Product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	85.398	MM	0.2594	572.71948	36.80141	94.80510
2	87.197	MM	0.1692	31.38249	3.09128	5.19490



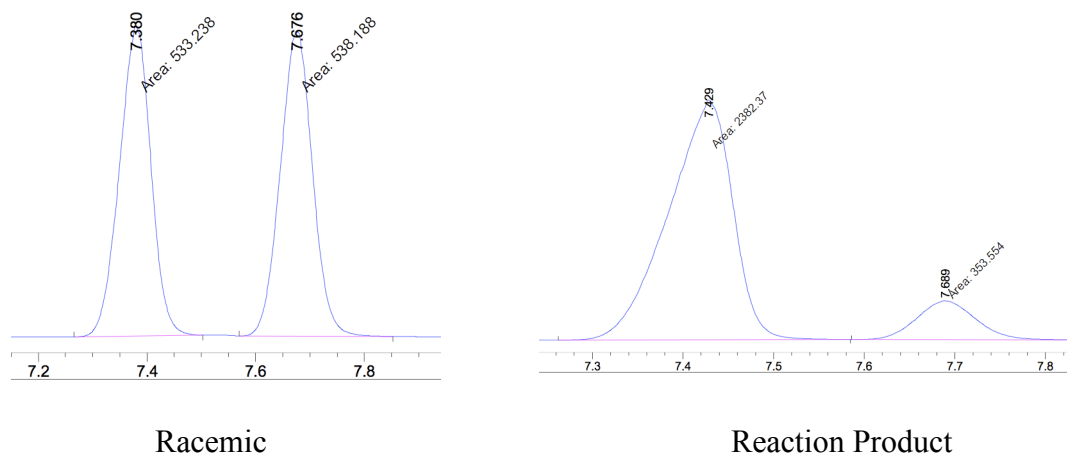
**(S)-1-(hexa-1,5-dien-3-yl)-4-(trifluoromethyl)benzene (3.58).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.44-2.56 (2H, m,  $\text{ArCHCH}_2\text{CH}=\text{CH}_2$ ), 3.43 (1H, app q,  $J = 7.5$  Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 4.97-5.11 (4H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  &  $\text{ArCHCH}=\text{CH}_2$ ), 5.69 (1H, dddd,  $J = 17.0$  Hz, 10.0 Hz, 7.0 Hz, 7.0 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.96 (1H, ddd,  $J = 17.5$ , 10.5, 7.0 Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 7.30 (2H, dd,  $J = 8.0$  Hz, 0.5 Hz,  $\text{ArH}$ ), 7.56 (2H, d,  $J = 8.0$  Hz,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  39.5, 49.4, 115.3, 116.7, 125.4 (q,  $J = 3.75$  Hz), 128.1, 135.9, 140.6, 147.7; IR (neat): 2922.3 (s), 2851.2 (m), 2166.2 (m), 2036.7 (m), 2019.9 (m), 2004.6 (m), 1961.1 (w), 1325.7 (w), 485.1 (w), 453.4 (m), 438.2 (m), 421.5 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{14}\text{Cl}$  [ $\text{M}+\text{H}$ ]: calculated: 227.1048, found: 227.1047;  $[\alpha]_D^{20} = +16.478$  ( $c = 0.985$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (20.3 mg, 60% yield).  $R_f = 0.63$  (pentane, stain in  $\text{KMnO}_4$ ).

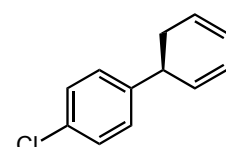
#### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

Chiral GLC (CD-GTA, Supelco, 100 °C, 25 psi) – analysis of the title compound.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.429	MM	0.0821	2382.36694	483.47037	87.07733
2	7.689	MM	0.0752	353.55417	78.31371	12.92267

 **(S)-1-chloro-4-(hexa-1,5-dien-3-yl)benzene (3.59).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 2.46 (2H, app dtd, *J* = 21.5 Hz, 14.0 Hz, 7.5 Hz, ArCHCH<sub>2</sub>CH=CH<sub>2</sub>), 3.34 (1H, app q, *J* = 7.5 Hz, ArCHCH=CH<sub>2</sub>), 4.96-5.08 (4H, m, CH<sub>2</sub>CH=CH<sub>2</sub> & ArCHCH=CH<sub>2</sub>), 5.69 (1H, app ddt, *J* = 17.0 Hz, 10.0 Hz, 7.0 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.94 (1H, ddd, *J* = 17.5, 10.5, 7.5 Hz, ArCHCH=CH<sub>2</sub>), 7.12 (2H, app dt, *J* = 8.5 Hz, 2.5 Hz, ArH), 7.27 (2H, app dt, *J* = 9.0 Hz, 2.5 Hz, ArH); <sup>13</sup>C NMR (125 Hz, CDCl<sub>3</sub>): δ 39.6, 48.9, 114.8, 116.5, 128.5, 129.1, 132.0, 136.2, 141.1, 142.1; IR (neat): 3078.8 (w), 2978.4 (w), 2925.5 (w, br), 1640.1 (w), 1490.9 (s), 1406.8 (w), 1091.7 (s), 1014.4 (m), 922.2 (m), 913.9 (s), 826.9 (m), 523.8 (w) cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>) for C<sub>12</sub>H<sub>14</sub>Cl

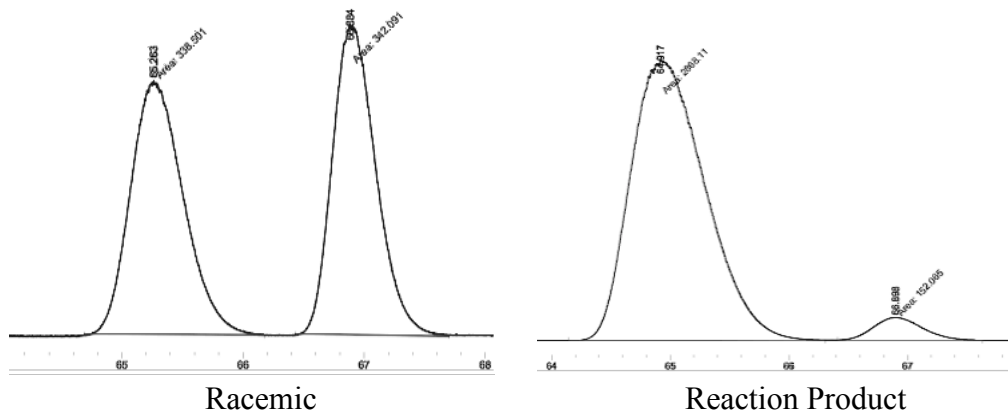
[M+H]<sup>+</sup>: calculated: 193.0784, found: 193.0793;  $[\alpha]_D^{20} = +24.816$  ( $c = 0.64$ , CHCl<sub>3</sub>).

The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (17.9 mg, 59% yield).  $R_f = 0.6$  (pentane, stain in KMnO<sub>4</sub>).

### ***Proof of Stereochemistry:***

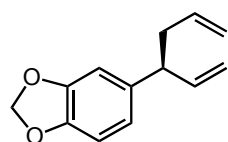
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

*Chiral GLC (CD-GTA, Supelco, 80 °C for 60 min, ramp 3 °C/min to 120 °C, 25 psi) – analysis of the title compound.*



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	64.917	MM	0.7236	2868.11475	66.06399	94.96504
2	66.898	MM	0.4733	152.06499	5.35460	5.03496





**(S)-5-(hexa-1,5-dien-3-yl)benzo[d][1,3]dioxole (3.60).**  $^1\text{H}$  NMR

(400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.38-2.50 (2H, m,  $\text{ArCHCH}_2\text{CH}=\text{CH}_2$ ), 3.28

(1H, app q,  $J = 7.6$  Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 4.95-5.06 (4H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  &

$\text{ArCHCH}=\text{CH}_2$ ), 5.71 (1H, app ddt,  $J = 16.8$  Hz, 12.5 Hz, 6.8 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.93

(2H, s,  $\text{OCH}_2\text{O}$ ), 5.93 (1H, ddd,  $J = 17.6$  Hz, 10.4 Hz, 7.6 Hz,  $\text{ArCHCH}=\text{CH}_2$ ), 6.64 (1H,

dd,  $J = 8.0$  Hz, 1.6 Hz,  $\text{ArH}$ ), 6.69 (1H, d,  $J = 1.6$  Hz,  $\text{ArH}$ ), 6.74 (1H, d,  $J = 8.0$  Hz,

$\text{ArH}$ );  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  39.8, 49.3, 100.8, 108.0, 108.1, 114.2, 116.1, 120.6,

136.5, 137.7, 141.6, 145.9, 147.6; IR (neat): 2895.2 (w, br), 1639.0 (w), 1503.0 (s),

1486.6 (s), 1440.4 (m), 1245.3 (s), 1039.9 (s), 913.7 (s), 809.8 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+)

for  $\text{C}_{13}\text{H}_{15}\text{O}_2$   $[\text{M}+\text{H}]$ : calculated: 203.1072, found: 203.1079;  $[\alpha]_D^{20} = +22.830$  ( $c = 0.69$ ,

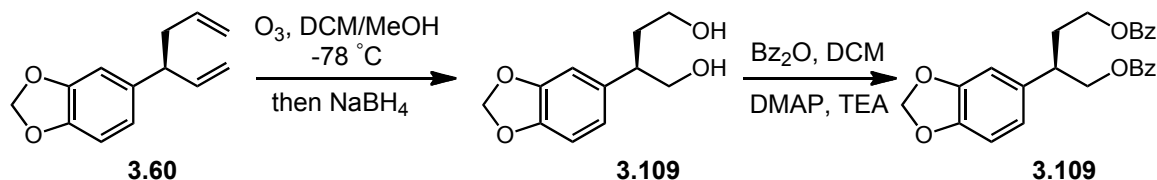
$\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (80:1 pentane:diethyl ether)

to afford a clear, colorless oil (23.4 mg, 83% yield).  $R_f = 0.32$  (60:1 pentane:diethyl

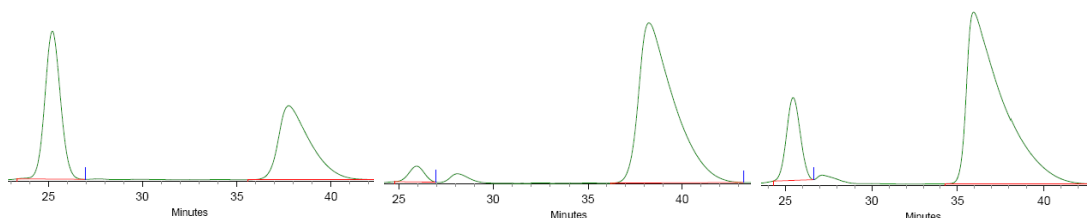
ether, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

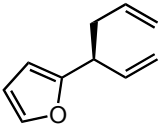
The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester for HPLC analysis, as depicted below. The analogous racemic material was prepared via the same route through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy.



Chiral HPLC (OD-R, Chiraldex, 1 mL/min, 3% isopropanol in hexanes, 220 nm) – analysis of the dibenzoate ester (**3.109**).



Racemic		Reaction Product		Reaction Product + Racemic	
Retention Time		Area	Area %	Height	Height %
25.947		9404811	4.10	166554	8.98
38.227		220148832	95.90	1687816	91.02

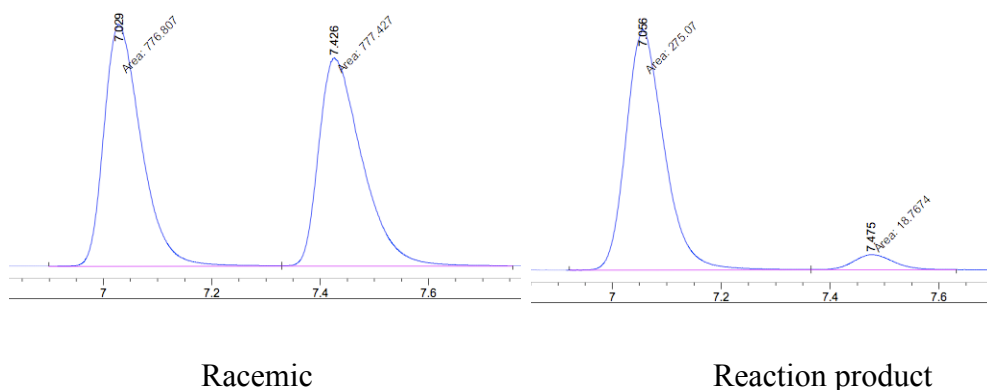

**(S)-2-(hexa-1,5-dien-3-yl)furan (3.62).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.43 (1H, ddd,  $J = 14.0, 7.5, 7.0$  Hz,  $\text{CHCH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.56 (1H, app dtt,  $J = 14.0, 7.0, 7.0, 1.5$  Hz,  $\text{CHCH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 3.47 (1H, app q,  $J = 7.5$  Hz,  $\text{FurCHCH}=\text{CH}_2$ ), 5.00-5.12 (4H, m,  $\text{CHCH}=\text{CH}_2$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.75 (1H, app ddt,  $J = 17.0, 10.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.87 (1H, ddd,  $J = 17.0, 10.5, 8.0$  Hz,  $\text{CHCH}=\text{CH}_2$ ), 6.04 (1H, dt,  $J = 3.0, 1.0$  Hz, Fur-**H**), 6.30 (1H, dd,  $J = 3.0, 2.0$  Hz, Fur-**H**), 7.34 (1H, dd,  $J = 2.0, 1.0$  Hz, Fur-**H**);  $^{13}\text{C}$  NMR (125 Hz,  $\text{CDCl}_3$ ):  $\delta$  37.7, 43.2, 105.1, 110.0, 115.7, 116.5, 132.9, 138.5, 141.2, 156.7; IR (neat): 2922.3 (s), 2851.9 (m), 1793.3 (w), 1727.3 (w), 1641.2 (w), 1462.8 (w), 1377.4 (w), 1274.1 (w), 1125.0 (w), 1077.4 (w), 823.4 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{13}\text{O}$   $[\text{M}+\text{H}]^+$ : calculated: 149.0966, found: 149.0968;  $[\alpha]_D^{20} = +32.168$  ( $c = 0.53$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel

(pentane) to afford a clear, light yellow oil (9.5 mg, 64% yield).  $R_f = 0.56$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

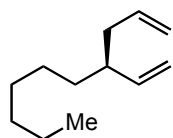
***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

*Chiral GLC (CD-GTA, Supelco, 70 °C, 25 psi) – analysis of the title compound.*



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.056	MF	0.0811	275.07043	56.54135	93.61302
2	7.475	FM	0.0875	18.76736	3.57612	6.38698

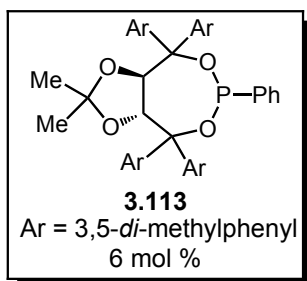
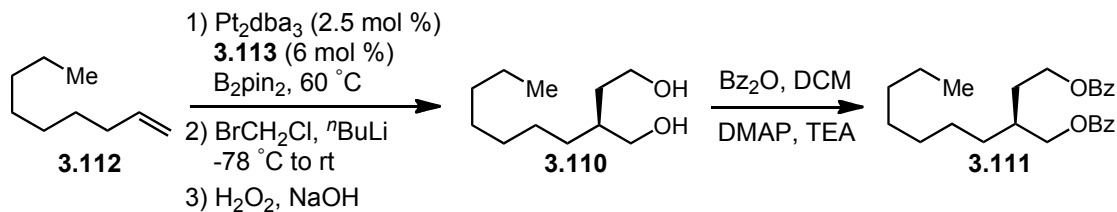
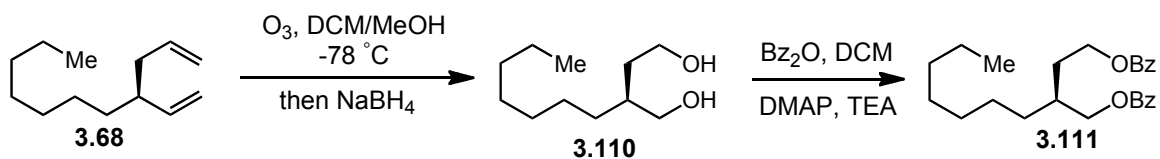


**(S)-4-vinylundec-1-ene (3.68).**  $^1\text{H}$  NMR (400 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.88 (3H, t,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 1.22-1.38 (12H, m,  $\text{CH}_3(\text{CH}_2)_6$ ), 2.01-2.14 (3H, m,  $\text{CHCH}=\text{CH}_2$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.92-5.02 (4H, m,  $\text{CHCH}=\text{CH}_2$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.58 (1H, ddd,  $J = 16.8$  Hz, 10.4 Hz, 8.0 Hz,  $\text{CHCH}=\text{CH}_2$ ), 5.76 (1H, app ddt,  $J = 17.2$  Hz, 10.4 Hz, 6.8 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  14.1, 22.7, 27.1, 29.3, 29.7, 31.9, 34.2, 39.5, 43.7, 114.1, 115.5, 137.2, 142.8; IR (neat): 3077.2 (w), 2957.1 (m), 2923.3 (s), 2854.2 (m), 1641.0 (s), 1465.1 (s), 1419.4 (w), 1378.1 (w), 992.6 (m), 909.4 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{25}$   $[\text{M}+\text{H}]$ : calculated: 181.1956, found: 181.1958;  $[\alpha]^{20}_{\text{D}} = -2.828$  ( $c = 0.76$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (14.4 mg, 80% yield of title compound). Mixture of branched to linear compounds: 11:1.  $R_f = 0.86$  (8:1 hexane: ethyl acetate).

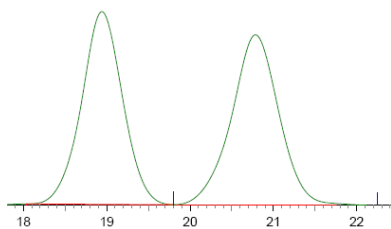
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by converting the allyl-allyl coupling product to a dibenzoate by ozonolysis/reduction and benzoate protection of the corresponding diol as shown below. *Via* chiral HPLC the resulting dibenzoate (**3.111**) was compared to racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by comparing the dibenzoate to authentic (*S*)-2-heptylbutane-1,4-diyl dibenzoate which was prepared by diboration/homologation/oxidation of 1-nonene, followed by dibenzoate protection as shown below.<sup>38</sup>

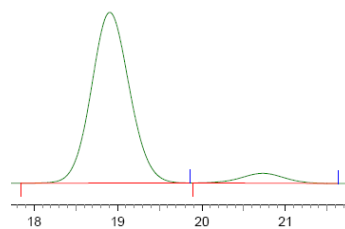
<sup>38</sup> Kliman, L. T.; Mlynarski, S. N.; Morken, J. P.; *J. Am. Chem. Soc.*, **2009**, *131*, 13210.



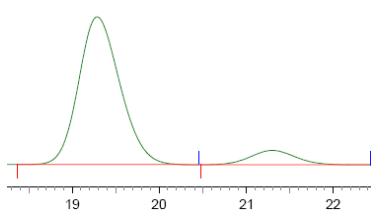
Chiral HPLC (OD-R, Chiralcel, 0.5 mL/min, 1% isopropanol, 220 nm) – analysis of 2-heptylbutane-1,4-diyl dibenzoate (**3.111**).



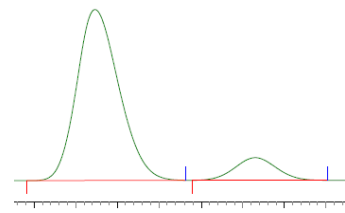
racemic



(*S*)-2-heptylbutane-1,4-diyl dibenzoate

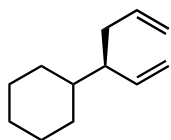


derived from reaction product



derivative + racemic

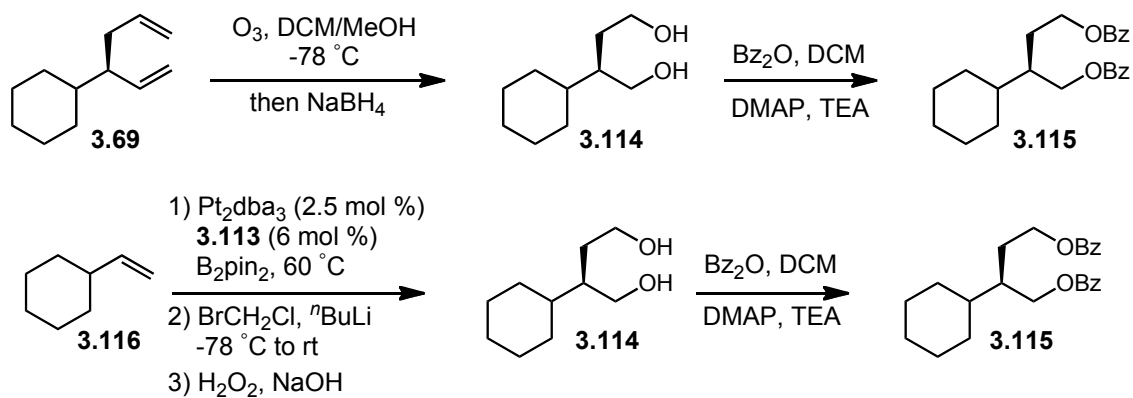
Retention Time	Area	Area %	Height	Height %
19.287	1013746288	90.51	30414501	91.21
21.297	106334887	9.49	2931252	8.79



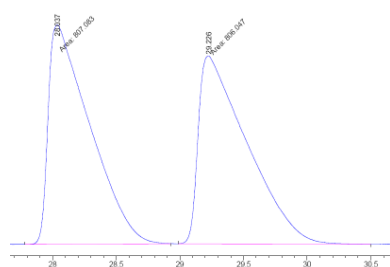
**(S)-hexa-1,5-dien-3-ylcyclohexane (3.69).**  $^1\text{H}$  NMR (500 Hz,  $\text{CDCl}_3$ ):  $\delta$  0.87-1.30 (6H, m,  $(\text{CH}_2)_3$ ), 1.61-1.73 (5H, m,  $\text{CH}_2\text{CHCH}_2$ ), 1.89 (1H, m,  $\text{CHCH}=\text{CH}_2$ ), 2.03-2.09 (1H, m,  $\text{CH}_a\text{CH}_b\text{CH}=\text{CH}_2$ ), 2.19-2.24 (1H, m,  $\text{CH}_a\text{CH}_b\text{CH}=\text{CH}_2$ ), 4.89-5.01 (4H, m,  $\text{CHCH}=\text{CH}_2$  &  $\text{CH}_a\text{CH}_b\text{CH}=\text{CH}_2$ ), 5.59 (1H, ddd,  $J = 19.5$  Hz,  $10.5$  Hz,  $9.5$  Hz,  $\text{CHCH}=\text{CH}_2$ ), 5.74 (1H, app ddt,  $J = 17.2$  Hz,  $10.4$  Hz,  $6.8$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  26.60, 26.63, 26.7, 29.4, 31.1, 36.4, 41.0, 49.8, 115.0, 115.2, 137.8, 140.9 ppm; IR (neat): 3075.2 (w), 2976.9 (w), 2921.2 (s), 2851.4 (s), 1639.8 (s), 1447.9 (m), 1419.4 (w), 993.9 (m), 908.2 (s), 704.9 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{21}$   $[\text{M}+\text{H}]$ : calculated: 165.1643, found: 165.1650;  $[\alpha]_D^{20} = -4.322$  ( $c = 0.62$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (10.3 mg, 63% yield of title compound). Mixture of branched to linear compounds: 10:1.  $R_f = 0.85$  (8:1 hexane: ethyl acetate, stain in  $\text{KMnO}_4$ ).

#### ***Proof of Stereochemistry:***

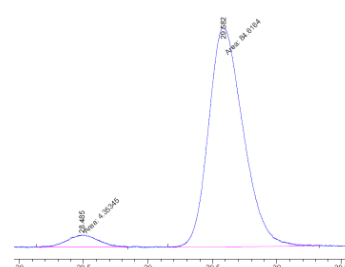
Enantioselectivity was determined by comparison of the title compound with authentic racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by converting the allyl-allyl coupling product to a dibenzoate (**3.115**), by ozonolysis/reduction and benzoate protection of the corresponding diol, as shown below. *Via* chiral HPLC the resulting dibenzoate was compared to (*R*)-2-cyclohexylbutane-1,4-diyl dibenzoate, which was prepared by diboration/homologation/oxidation of vinylcyclohexane, followed by dibenzoate protection as shown below.<sup>38</sup>



Chiral GLC ( $\beta$ -dex, Supelco,  $80^\circ\text{C}$ , 25 psi) - analysis of title compound



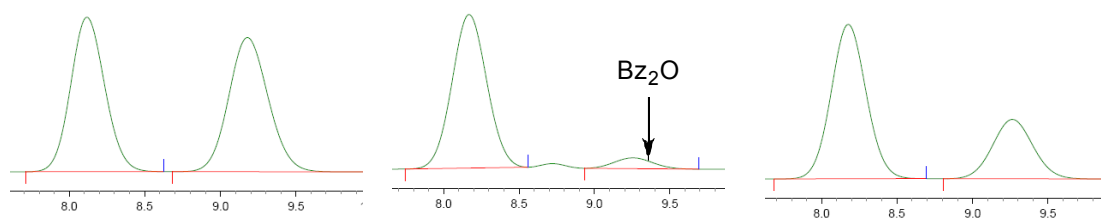
racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	28.486	MM	0.2998	4.78294	2.65896e-1	5.32266
2	29.580	MM	0.3141	85.07700	4.51380	94.67734

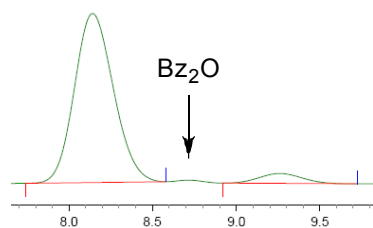
*Chiral HPLC (OD-R, Chiralcel, 1 mL/min, 1% isopropanol, 220 nm) – analysis of 2-cyclohexylbutane-1,4-diyl dibenzoate (3.115).*



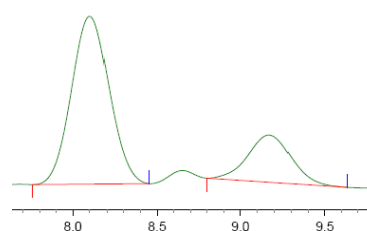
racemic

derived from reaction product

derivative + racemic



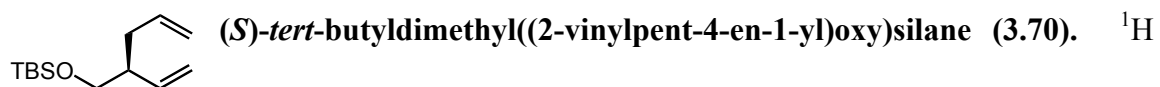
(*R*)-2-cyclohexylbutane-1,4-diyl dibenzoate



(*R*)-2-cyclohexylbutane-1,4-diyl

dibenzoate + racemic



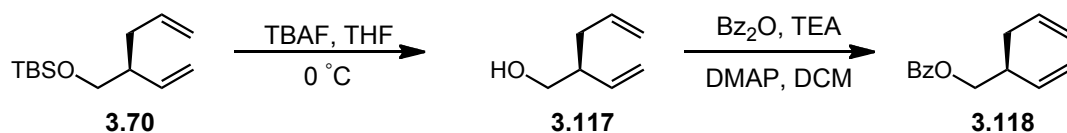


NMR (500 MHz, CDCl<sub>3</sub>): δ 0.04 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), 0.89 (9H, s, Si(C(CH<sub>3</sub>)<sub>3</sub>)), 2.04-2.09 (1H, m, CHCH<sub>A</sub>H<sub>B</sub>CH=CH<sub>2</sub>), 2.24-2.33 (2H, m, CHCH<sub>A</sub>H<sub>B</sub>CH=CH<sub>2</sub> and CH<sub>2</sub>CH<sub>A</sub>H<sub>B</sub>), 3.50-3.57 (2H, m, SiOCH<sub>2</sub>), 4.98-5.06 (4H, m, CHCH=CH<sub>2</sub> & CH<sub>2</sub>CH=CH<sub>2</sub>), 5.65-5.70 (1H, m, CHCH=CH<sub>2</sub>), 5.78 (1H, app ddt, *J* = 17.0 Hz, 10.5 Hz, 7.0 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>); <sup>13</sup>C NMR (125 Hz, CDCl<sub>3</sub>): δ -5.4, -5.4, 18.3, 25.9, 35.3, 46.0, 65.9, 115.4, 115.8, 136.9, 139.7; IR (neat): 3077.8 (w), 2955.7 (m), 2928.7 (m), 2857.2 (m), 1730.7 (m), 1641.3, (w), 1470.9 (m), 1253.4 (s), 1097.4 (s), 992.6, (m), 1097.4 (s), 912.0 (s), 834.1 (s), 773.7 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>13</sub>H<sub>27</sub>OSi [M+H]: calculated: 227.1831, found: 227.1831; [α]<sub>D</sub><sup>20</sup> = +6.254 (*c* = 1.227, CHCl<sub>3</sub>).

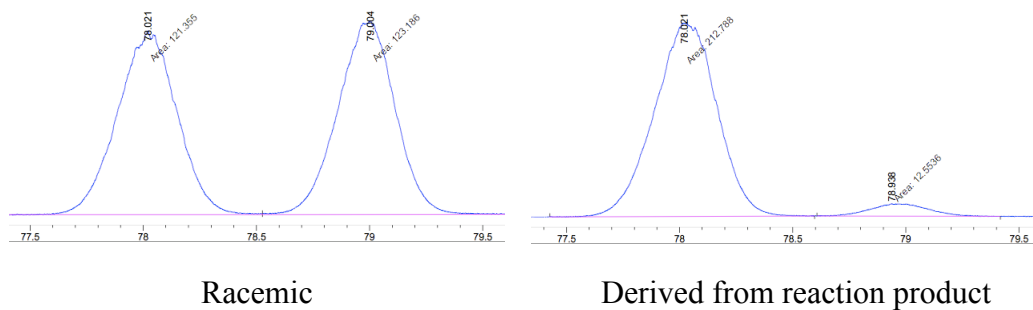
The crude reaction mixture was purified on silica gel (pentane, then 50:1 pentane: ether) to afford a clear, colorless oil (20.6 mg, 91% yield). *R*<sub>f</sub> = 0.76 (8:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

### ***Proof of Stereochemistry:***

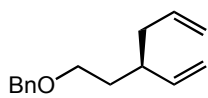
Enantioselectivity was determined by converting the allyl-allyl coupling product to a benzoate (**3.118**) by deprotection of TBS group and benzoate protection of the corresponding alcohol as shown below. *Via* chiral GLC the resulting benzoate was compared to racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy.



*Chiral GLC (CD-GTA, Supelco, 100 °C, 60 min, then 1°C/min to 130 °C, 25 psi) – analysis of benzoate (3.118).*



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	78.021	MM	0.3222	212.78847	11.00840	94.42910
2	78.938	MM	0.3000	12.55359	6.97340e-1	5.57090

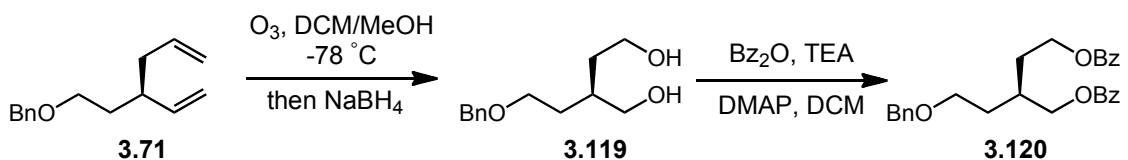


**(*R*)-(((3-vinylhex-5-en-1-yl)oxy)methyl)benzene (3.71).**  $^1\text{H}$  NMR

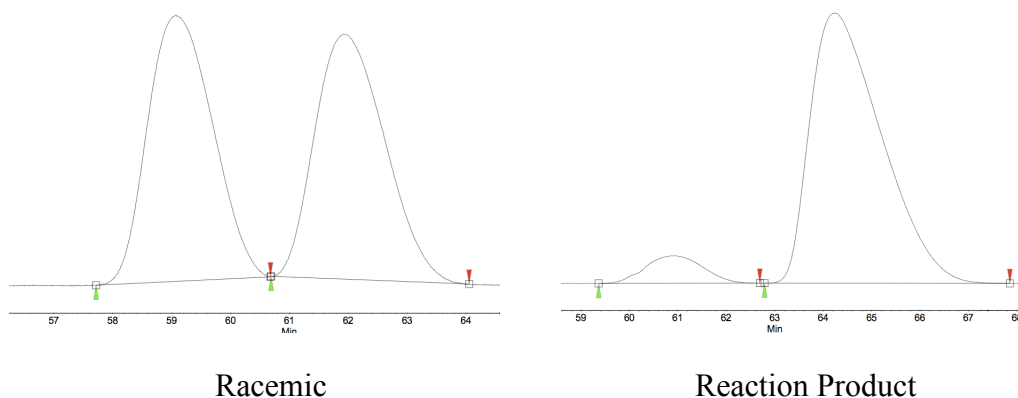
(400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.49-1.57 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}=\text{CH}_2$ ), 1.75-1.83 (1H, m,  $\text{CH}_\text{B}$   $\text{HCH}=\text{CH}_2$ ), 2.05-2.19 (2H, m,  $\text{BnOCH}_2\text{CH}_2$ ), 2.28 (1H, app dtd,  $J = 13.6$  Hz, 8.4 Hz, 5.2 Hz,  $\text{CHCH}=\text{CH}_2$ ), 3.42-3.53 (2H, m,  $\text{BnOCH}_2$ ), 4.49 (2H, d,  $J = 2.0$  Hz,  $\text{PhCH}_2\text{O}$ ), 4.94-5.04 (4H, m,  $\text{CHCH}=\text{CH}_2$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.59 (1H, ddd,  $J = 17.2$  Hz, 10.4 Hz, 8.8 Hz,  $\text{CHCH}=\text{CH}_2$ ), 5.76 (1H, app dtt,  $J = 20.8$  Hz, 12.0 Hz, 5.6 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 7.25-7.34 (5H, m,  $\text{PhH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  34.0, 39.5, 40.4, 68.3, 72.9, 114.8, 115.9, 127.5, 127.6, 128.3, 136.7, 138.6, 141.9; IR (neat): 3074.5 (w), 2926.0 (m), 2856.6 (m), 1640.7, (m), 1495.9 (w), 1453.9 (m), 1419.2 (w), 1363.5, (m), 1204.2 (w), 1101.6 (s), 1028.0 (w), 994.4 (m), 912.1 (s), 735.0 (s), 697.1 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{21}\text{O}$  [ $\text{M}+\text{H}$ ]: calculated: 217.1592, found: 217.1590;  $[\alpha]_\text{D}^{20} = -11.355$  ( $c = 1.18$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (100:1 hexanes: ethyl acetate) to afford a clear, colorless oil (24.3 mg, 75% yield of title compound) as a mixture of coupling product and diene (90:10).  $R_f = 0.35$  (100:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

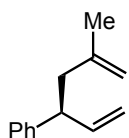
The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester (**3.120**) for HPLC analysis, as depicted below. The analogous racemic material was prepared via the same route through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy.



*Chiral SFC (AD-H, Chiralpak, 220nm, 1 mL/min, 1% MeOH, ramped 0.1% per minute to 5% MeOH, 150 bar, 50 °C) – analysis of the dibenzoate ester (**3.120**).*



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[ $\mu\text{V}$ ]	[ $\mu\text{V}\cdot\text{Min}$ ]	[%]
1	UNKNOWN	59.36	60.90	62.69	0.00	7.64	493.9	682.7	7.636
2	UNKNOWN	62.79	64.23	67.85	0.00	92.36	4850.2	8258.5	92.364
Total						100.00	5344.2	8941.3	100.000

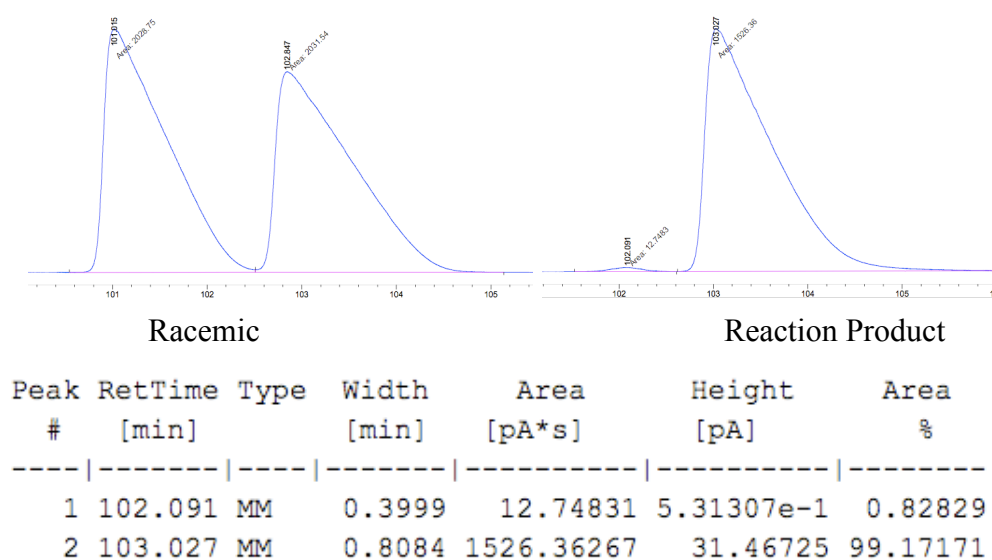


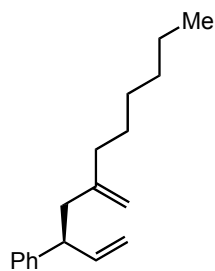
**(S)-(5-methylhexa-1,5-dien-3-yl)benzene (3.73).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.70 (3H, s,  $\text{CH}_3$ ), 2.45 (2H, app dtd,  $J = 14.0$  Hz, 14.0 Hz, 8.0 Hz,  $\text{CHCH}_2\text{CH}=\text{CH}_2$ ), 3.51 (1H, app q,  $J = 7.5$  Hz,  $\text{PhCHCH}_2$ ), 4.64 (1H, m,  $\text{MeC}=\text{CH}_\text{A}$ ), 4.72 (1H, m,  $\text{MeC}=\text{CH}_\text{B}$ ), 4.98-5.04 (2H, m,  $\text{CHCH}=\text{CH}_2$ ), 5.97 (1H, ddd,  $J = 17.0$  Hz, 10.0 Hz, 7.0 Hz,  $\text{CHCH}=\text{CH}_2$ ), 7.18-7.21 (3H, m,  $\text{PhH}$ ), 7.26-7.32 (2H, m,  $\text{PhH}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.4, 44.0, 47.8, 112.3, 114.1, 126.2, 127.7, 128.4, 141.8, 143.4, 144.0; IR (neat): 3075.8 (w), 3027.8 (w), 2970.2 (w), 1637.6 (w), 1601.2 (w), 1493.8 (w), 1451.7 (w), 1414.6 (m), 1373.9 (w), 990.8 (m), 911.9 (s), 887.6 (s), 752.2 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{17}$   $[\text{M}+\text{H}]$ : calculated: 173.1330, found: 173.1330;  $[\alpha]_\text{D}^{20} = +27.681$  ( $c = 0.987$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (13.6 mg, 79% yield).  $R_f = 0.48$  (18:1 hexane: ethyl acetate, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling. The absolute stereochemistry was assigned by analogy.

*Chiral GLC ( $\beta$ -dex, Supelco, 80 °C, 25 psi) - analysis of title compound.*

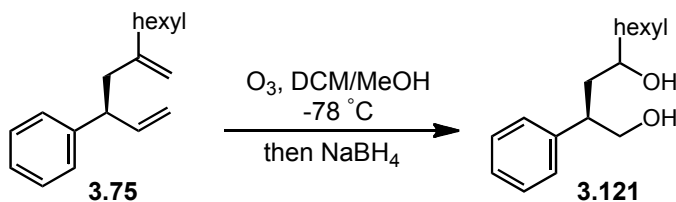




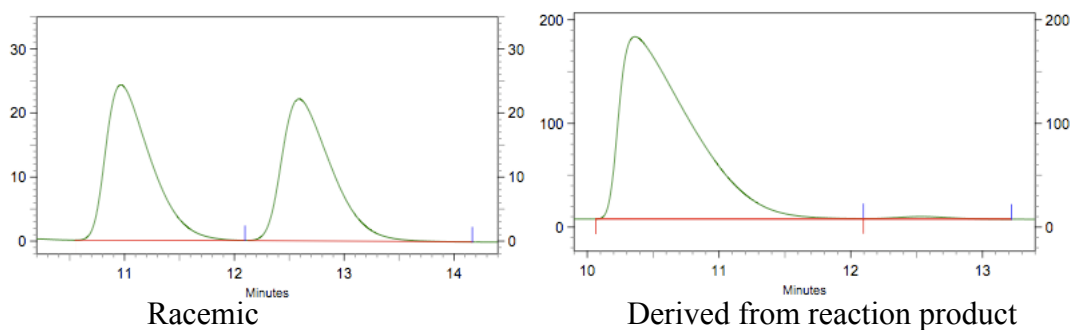
**(S)-(5-methyleneundec-1-en-3-yl)benzene (3.75).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.89 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.24-1.44 (8H, m,  $(\text{CH}_2)_4\text{CH}_3$ ), 1.97 (2H, t,  $J = 7.6$  Hz,  $(\text{CH}_2)_4\text{CH}_2\text{CC}=\text{CH}_2$ ), 2.44 (2H, d,  $J = 7.6$  Hz,  $\text{PhCHCH}_2\text{C}=\text{CH}_2$ ), 3.49 (1H, app q,  $J = 7.6$  Hz,  $\text{PhCH}$ ), 4.67 (1H, s,  $\text{C}=\text{CH}_a\text{H}_b$ ), 4.73 (1H, s,  $\text{C}=\text{CH}_a\text{H}_b$ ), 4.99 (1H, dt,  $J = 17.6, 1.2$  Hz,  $\text{CH}=\text{CH}_{trans}$ ), 5.02 (1H, dt,  $J = 10.4, 1.2$  Hz,  $\text{CH}=\text{CH}_{cis}$ ), 5.97 (1H, ddd,  $J = 17.6, 10.4, 7.2$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.17-7.21 (3H, m,  $\text{PhH}$ ), 7.28-7.31 (2H, m,  $\text{PhH}$ );  $^{13}\text{C}$  NMR (100 Hz,  $\text{CDCl}_3$ ):  $\delta$  13.0, 14.4, 27.9, 29.4, 32.1, 36.3, 42.4, 48.1, 111.4, 114.5, 126.5, 128.0, 128.7, 142.2, 144.5, 147.7; IR (neat): 3670.0 (w), 3028.1 (w), 2956.3 (m), 2926.8 (s), 2856.4 (m), 1642.9 (w), 1493.1 (w), 1453.0 (m), 1378.1 (w), 1074.4 (w), 990.6 (w), 912.3 (m), 891.0 (m), 753.2 (m), 673.0 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{18}\text{H}_{27}$   $[\text{M}+\text{H}]$ : calculated: 243.2113, found: 243.2105;  $[\alpha]_D^{20} = +24.191$  ( $c = 0.75$ ,  $\text{CHCl}_3$ ). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (18.9 mg, 78% yield).  $R_f = 0.68$  (8:1 hexanes: ethyl acetate, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

Enantioselectivity was determined by converting the allyl-allyl coupling product to a diol by ozonolysis/reduction. *Via* chiral HPLC the resulting diol (**3.121**) was compared to racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy.



*Chiral HPLC (AS-H, Chiralpak, 220nm, 1 mL/min, 2% isopropanol) – analysis of the diol (3.121).*

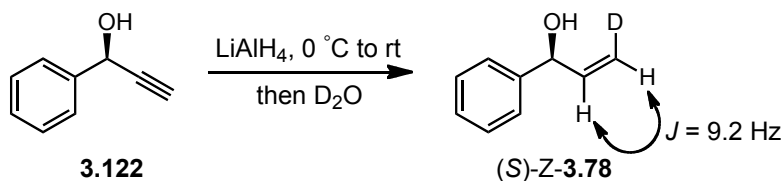


Retention Time	Area	Area %	Height	Height %
10.363	110295188	98.88	2952849	98.61
12.533	1246973	1.12	41595	1.39



## 6. Deuterium-Labeling Study

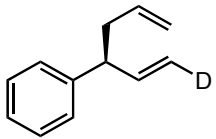
**Preparation of (*S*)-(-)-*tert*-butyl *cis*-3-[<sup>2</sup>H]-1-phenylprop-2-enyl carbonate.** From the deuterated allylic alcohol,<sup>39</sup> synthesized from commercially available (*S*)-1-phenylprop-2-yn-1-ol (**3.122**), >95:5 er, procedure B was followed.

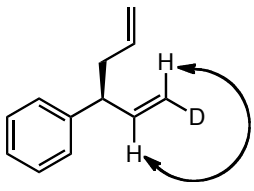


**(*S*)-(-)-*tert*-butyl *cis*-3-[<sup>2</sup>H]-1-phenylprop-2-enyl carbonate ((*S*)-Z-3.78).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.47 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 5.24 (1H, app dt, *J* = 9.2, 4.0 Hz, CH=CHD), 6.01-6.04 (2H, m, CH=CHD & PhCHO<sub>Boc</sub>), 7.26-7.38 (5H, m, PhH); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 27.8, 71.2, 82.3, 116.9 [t, <sup>1</sup>*J*(C, <sup>2</sup>H) = 23.8 Hz], 127.0, 128.2, 128.5, 136.1, 138.7, 152.7; IR (neat): 2980.8 (w), 2933.3 (w), 1739.3 (s), 1495.0 (w), 1394.3 (m), 1312.3 (s), 1273.8 (s), 1252.5 (s), 1086.0 (m), 966.7 (w), 894.8 (m), 698.8 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>9</sub>H<sub>8</sub>D [M-OBoc]: calculated: 118.0767, found: 118.0768; [α]<sub>D</sub><sup>20</sup> = -29.776 (*c* = 0.97, CHCl<sub>3</sub>). The crude reaction mixture was purified on silica gel (50:1 hexanes: ethyl acetate) to afford a clear, light yellow oil (93% yield). *R*<sub>f</sub> = 0.56 (8:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

<sup>39</sup> Kang, M. J.; Jang, J. S.; Lee, S. G. *Tetrahedron Lett.* **1995**, 36, 8829.

**Allyl-allyl coupling of deuterium-labeled starting material utilizing allylboronic acid pinacol ester:** The representative procedure for allyl-allyl coupling was applied.

 **(*S*)-trans-1-[<sup>2</sup>H1]-hexa-1,5-dien-ylbenzene ((*S*)-*E*-3.79).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 2.49 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.36 (1H, app q, *J* = 7.0 Hz, PhCH), 4.96-5.04 (3H, m, CH=CH<sub>2</sub> & CH=CHD), 5.73 (1H, ddt, *J* = 17.5, 10.0, 7.0 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.98 (1H, dd, *J* = 17.5, 7.5 Hz, CHCH=CHD), 7.19-7.32 (3H, m, Ph-H), 7.29-7.38 (2H, m, Ph-H); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>): δ 39.7, 49.6, 114.1 [t, <sup>1</sup>*J*(C, <sup>2</sup>H) = 23.8 Hz], 116.1, 126.3, 127.7, 128.4, 136.6, 141.4, 143.7; IR (neat): 3077.2 (w), 3028.3 (w), 3003.2 (w), 2924.5 (w, br), 2857.1 (w, br), 1640.2 (w), 1600.4 (w), 1451.8 (w), 1415.7 (w), 979.3 (m), 911.7 (s), 747.1 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>12</sub>H<sub>14</sub>D [M+H]: calculated: 160.1237, found: 160.1233; [α]<sub>D</sub><sup>20</sup> = +18.858 (*c* = 0.88, CHCl<sub>3</sub>). The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (11.7 mg, 77% yield). *R*<sub>f</sub> = 0.79 (8:1 hexanes: ethyl acetate, stain in KMnO<sub>4</sub>).

 *J* = 17.5 Hz

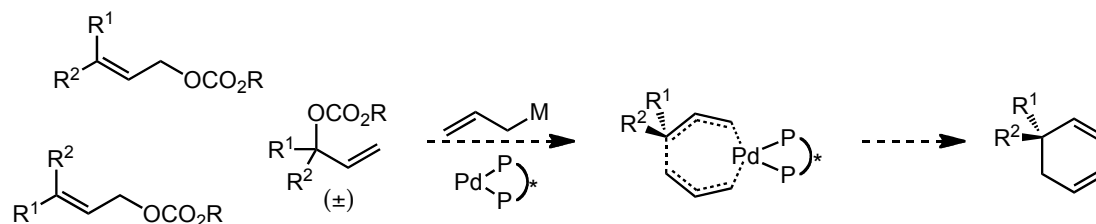
## Chapter IV

# Enantioselective Construction of All-Carbon Quaternary Centers through Pd-Catalyzed Allyl-Allyl Cross-Coupling

### I. INTRODUCTION

All-carbon quaternary stereogenic centers are ubiquitous motifs in natural products and pharmaceutical agents. The catalytic enantioselective construction of quaternary centers poses a particular challenge for organic synthesis, likely due to the following two reasons: (1) the steric repulsion between the carbon substituents increases the barriers for the carbon-carbon bond formation, (2) efficient enantiocontrol is difficult because of the weak discrimination between the enantiotopic faces of substrates and intermediates. Encouraged by the success of Pd-catalyzed branch- and enantioselective allyl-allyl cross-coupling described in Chapter III, it was of great interest to determine whether this reaction could be extended to the more demanding case of quaternary center assembly. We envisioned that this method of quaternary center construction would benefit from the rapid isomerization of  $\pi$ -allyl-palladium complexes. Thus, easily accessed racemic tertiary allylic alcohol derivatives as well as their geometric isomers can be employed as substrates. (Scheme 4.1)

**Scheme 4.1**



## II. BACKGROUND

**A. Catalytic Enantioselective Construction of All-Carbon Quaternary Centers through Allylic Substitutions.** The invention of catalytic methods for enantioselective synthesis is one of the foremost achievements of chemistry. Highly efficient and practical catalytic enantioselective reduction and oxidation have been developed and extensively studied, however, far fewer catalytic methods for forming carbon-carbon bonds in an enantioselective fashion have been invented to date. With regard to catalytic enantioselective construction of all carbon quaternary centers, the reliable synthetic methods are even more limited.

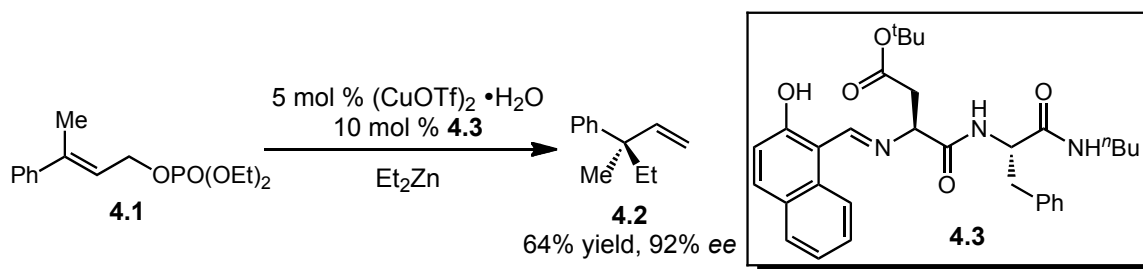
Among this subset of catalysis, the asymmetric Diels-Alder reaction is one of the most powerful transformations, wherein 1,1-disubstituted dienophiles are utilized to form quaternary centers. Chiral Lewis acids are often employed as catalysts for prochiral face selection.<sup>1</sup> Intramolecular Heck reaction is a broadly applicable method for simultaneously forming rings and all-carbon stereocenters as well, in which high levels of

<sup>1</sup> For representative examples see: (a) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 798. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. For a review on enantioselective Diels-Alder reaction: (c) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

enantiocontrol have been shown with appropriate chiral phosphine ligands.<sup>2</sup> Taking advantage of catalytically generated chiral carbon nucleophiles, enolate  $\alpha$ -arylation<sup>3</sup>,  $\alpha$ -allylation<sup>4</sup> and  $\alpha$ -conjugate addition<sup>5</sup> have proven to be valuable strategies. In a complementary fashion, the conjugate addition to trisubstituted enones<sup>6</sup> and allylic substitution<sup>7</sup> are of great importance.

Utilizing copper-based catalysis, allylic  $S_N2'$  substitution of trisubstituted olefins can afford olefin products bearing all-carbon quaternary centers in high yield and excellent optical purity. In 2001, Hoveyda and co-workers disclosed the use of peptide ligands in the Cu-catalyzed allylic alkylations of allylphosphates, accomplishing excellent regio- and enantiocontrol.<sup>8</sup> Upon ligand modification, higher enantioselectivity was achieved with dialkylzinc reagents as the nucleophilic partner (Scheme 4.2).<sup>9</sup>

**Scheme 4.2**



<sup>2</sup> For a review on enantioselective Heck reaction: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

<sup>3</sup> For reviews: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

<sup>4</sup> For reviews: (a) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476. (b) Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952.

<sup>5</sup> For representative examples: Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.

<sup>6</sup> For a review: Hawner, C.; Alexakis, A. *Chem. Comm.* **2010**, *46*, 7295.

<sup>7</sup> For a review: Falcicola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765.

<sup>8</sup> Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456.

<sup>9</sup> Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676.

In addition to the peptide-based ligands, bidentate diaminocarbene-based ligands (NHCs, e.g. **4.7** and **4.8** as their complexes with Ag) were disclosed as efficient chiral promoters for Cu-catalyzed allylic substitution. The new set of catalysts is significantly more effective than the above-mentioned ligands (e.g. **4.3**), allowing highly selective substitutions of trisubstituted olefins with much lower catalyst loading. Impressively under Cu-NHC catalytic systems, several classes of organometal nucleophiles can be utilized, allowing alkylation,<sup>10</sup> alkenylation,<sup>11</sup> alkynylation<sup>12</sup> as well as arylation<sup>13</sup> with high levels of regio- and enantiocontrol.

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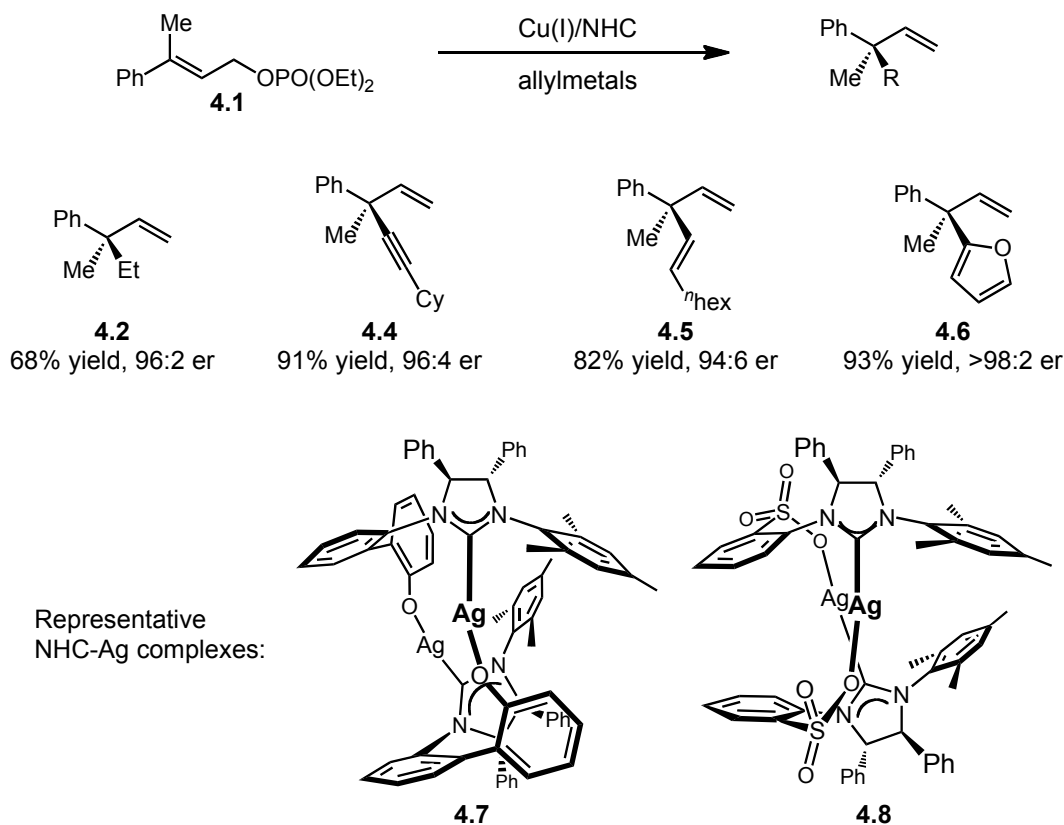
<sup>10</sup> Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.

<sup>11</sup> Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315.

<sup>12</sup> Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778.

<sup>13</sup> Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8370.

**Scheme 4.3**



Although Cu-catalyzed allylic substitution allows for the synthesis of all-carbon quaternary centers, isomerically pure allylic electrophiles (e.g. **4.1**) are generally required to ensure the high enantioselectivity. Thus the application of these methods is sometimes limited as a consequence of the difficulties associated with obtaining isomerically pure trisubstituted olefins.

**B.  $\pi$ - $\sigma$ - $\pi$  Isomerization of Allylmetal Complexes.** The necessity of isomerically pure substrates in Cu-catalyzed allylic substitution is a result of slow  $\pi$ - $\sigma$ - $\pi$  isomerization of Cu-allyl complexes relative to carbon-carbon bond formation. Other

metals exhibiting slow isomerization include W,<sup>14</sup> Ru<sup>15</sup> and Ir.<sup>16</sup> These metals are unique because branch-selective allylation can be achieved through reaction with either internal or terminal allylic electrophiles. In contrast, Mo<sup>17</sup> and Pd<sup>18</sup> allyl complexes undergo rapid  $\pi$ - $\sigma$ - $\pi$  equilibration under most reaction conditions, and branch-selectivity can be achieved under appropriate conditions. This property allows for mixtures of stereoisomers and regioisomers to ultimately deliver the same allylation products for a given catalyst system. In particular, Pd-catalysis has been extensively studied in the regio- and enantioselective substitution of allylic electrophiles to generate tertiary centers. However, presumably because the  $\pi$ - $\sigma$ - $\pi$  isomerization of  $\eta^3$ -pseudoprenylpalladium (when  $R^1 \neq H$  and  $R^2 \neq H$ , in **4.I** and **4.III**) is slower than that of the less substituted  $\eta^3$ -allylpalladium complexes (when  $R^1$  or  $R^2 = H$ , in **4.I** and **4.III**, Scheme 4.4),<sup>19</sup> there are far fewer examples of using this strategy to synthesize quaternary centers.

<sup>14</sup> (a) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462. (b) Prétôt, R.; Lloyd-Jones, G. C.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035.

<sup>15</sup> Trost, B. M.; Fraise, P. L.; Ball, Z. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1059.

<sup>16</sup> (a) Takeuchi, R.; Shiga, N. *Org. Lett.* **1999**, *1*, 265. (b) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (c) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569. (d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrach, K. *Chem. Eur. J.* **2006**, *12*, 3596. (e) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918. (f) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. Under appropriate conditions, isomerization with Ir can be rapid. See: (g) Bartels, B.; Helmchen, G. *Chem. Comm.* **1999**, 741.

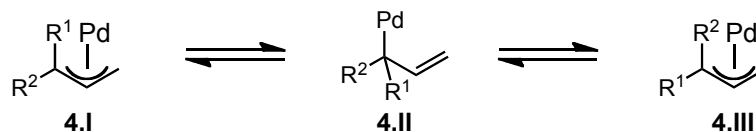
<sup>17</sup> (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Starý, I.; Langer, V.; Spoor, P.; Vinader, V.; Kočovský, P. *Chem. Eur. J.* **2006**, *12*, 6910. (c) Trost, B. M.; Zhang, Y. *Chem. Eur. J.* **2010**, *16*, 296.

<sup>18</sup> For a review: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

<sup>19</sup> Regioselectivity differences between geranyl and neryl geometrical isomers have been reported: (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. The slow interconversion of  $\eta^3$ -geranylpalladium and  $\eta^3$ -nerylpalladium complexes has previously been implicated: (b) Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275.



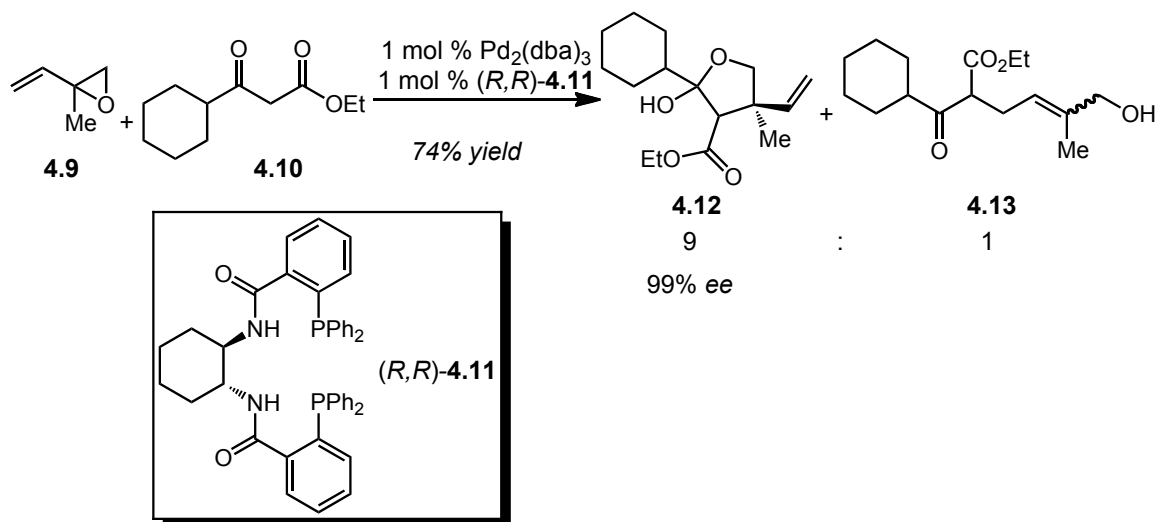
#### Scheme 4.4



In 2001, Trost reported a Pd-catalyzed enantioselective addition of  $\beta$ -ketoesters to isoprene monoepoxide, which provided quaternary carbon centers with high levels of enantiocontrol.<sup>20</sup> In contrast to the common  $S_N2'$  reactivity of isoprene monoepoxides under palladium catalysis due to electronic effects of the epoxide oxygen, 1,2-adducts are observed as the major products (Scheme 4.5). The authors hypothesized that with appropriate bulky diphosphine ligands (e.g. **4.11**), a beneficial interaction between the epoxide oxygen and  $\beta$ -ketoesters can be achieved, which allows for nucleophilic attack onto the adjacent carbon to form the normally disfavored 1,2-adducts. It has also been observed that under conditions which promote interconversion of  $\pi$ -allylpalladium complexes, regioselectivity is much higher. It was hypothesized by the authors that one diastereomeric  $\pi$ -allylpalladium intermediate delivers the 1,2-product whereas the other provides the 1,4-product.

<sup>20</sup> Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907.

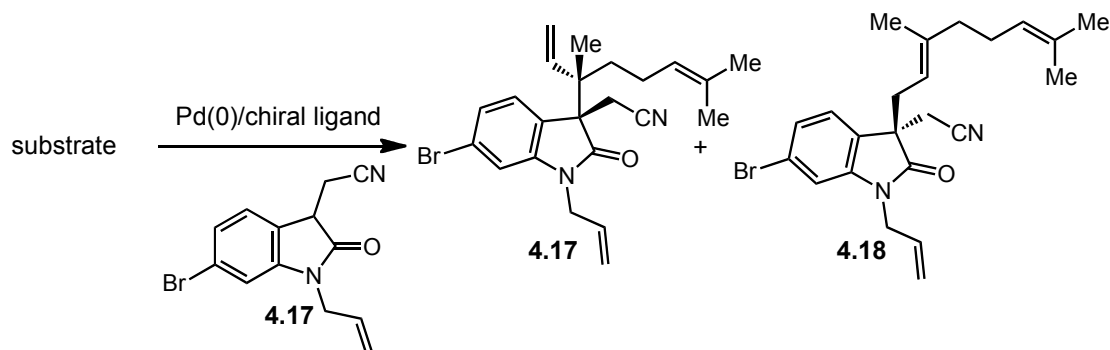
**Scheme 4.5**

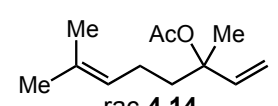
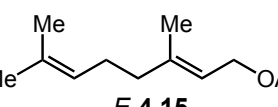
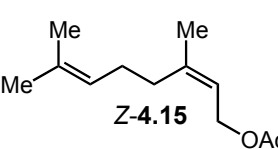


More recently, the Trost group described an enantioselective prenylation and reverse-prenylation of oxindoles.<sup>21</sup> This reaction proceeds in stereospecific manner wherein the reaction outcome is almost completely determined by the isomeric form of the starting material. As shown in Table 4.1, under the same reaction condition, acetates derived from geraniol (*E*-**4.15**) and nerol (*Z*-**4.15**) provide two distinct substitution products (**4.17** and **4.18**), whereas the corresponding racemic tertiary allylic acetates (rac-**4.14**) deliver both products in a 1:1 ratio. These results imply very slow  $\pi$ - $\sigma$ - $\pi$  isomerization between  $\eta^3$ -geranylpalladium and  $\eta^3$ -nerylpalladium complexes and each of them leads to a different reaction mode.

<sup>21</sup> Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, 133, 7328.

**Table 4.1 Pd-Catalyzed Prenylation and Reverse-Prenylation**

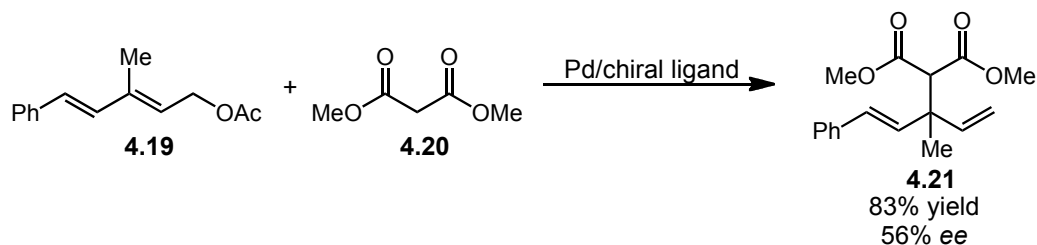


substrate	4.17 : 4.18	%yield	%ee
 <b>rac-4.14</b>	1:1	46( <b>4.17</b> )	90( <b>4.17</b> )
 <b>E-4.15</b>	1:>100	76( <b>4.18</b> )	91( <b>4.18</b> )
 <b>Z-4.15</b>	>100:1	92( <b>4.17</b> )	91( <b>4.17</b> )

Lately, the assembly of all-carbon quaternary center through the substitution of the corresponding 1,1-disubstituted electrophiles has been described in the Pd-catalyzed enantioselective allylic alkylation of dieny acetates.<sup>22</sup> Regrettably, the only example for quaternary center construction, as shown in Scheme 4.6, suffers from poor enantioselectivity. This is most likely a result of ineffective prochiral facial selectivity from the chiral ligand employed or, perhaps, from slow isomerization of  $\pi$ -allylpalladium intermediates involved in the transformation.

<sup>22</sup> Zheng, W. H.; Sun, N.; Hou, X. L. *Org. Lett.* **2005**, 7, 5151.

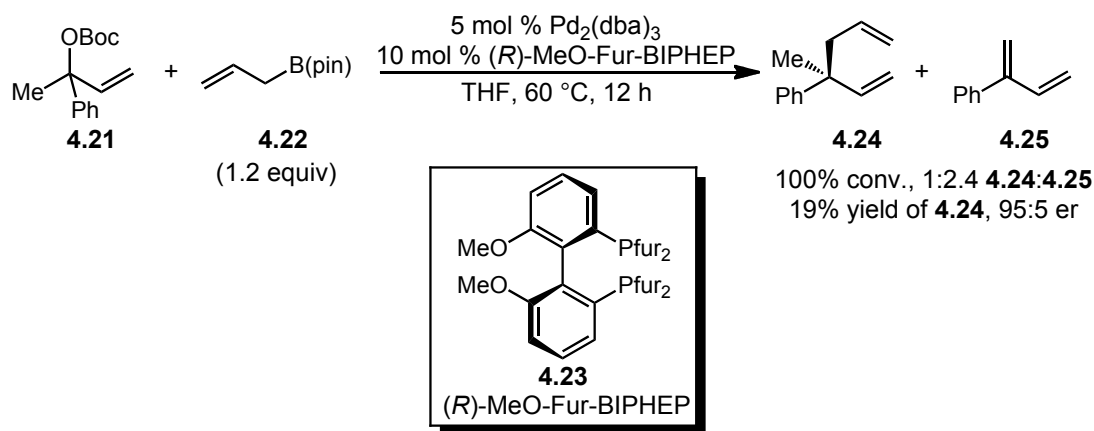
### Scheme 4.6



## III. THE DEVELOPMENT OF QUATERNARY CARBON CENTER FORMATION THROUGH ALLYL-ALLYL CROSS-COUPLING

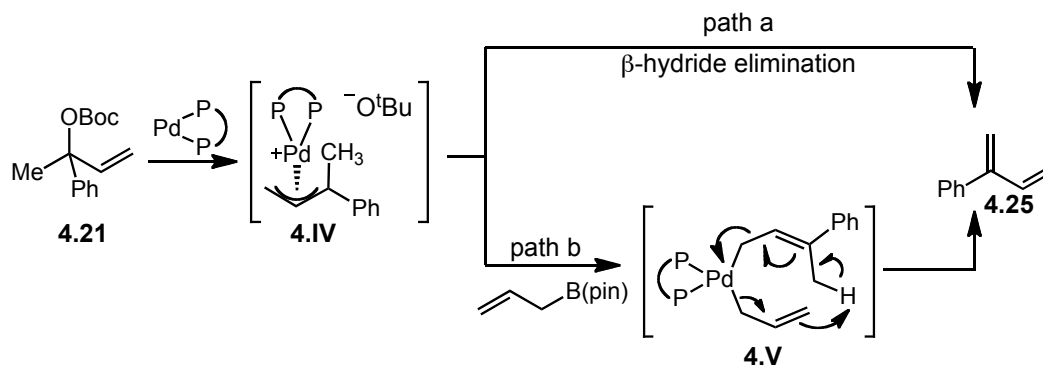
**A. Initial Reaction Condition Optimization.** To initiate these studies, the readily synthesized racemic allylic carbonate **4.21** was subjected to the standard allyl-allyl cross-coupling condition as described in Chapter III: 5 mol %  $\text{Pd}_2(\text{dba})_3$ , 10 mol % MeO-Fur-BIPHEP (**4.23**) and allylB(pin) (**4.22**) in THF. As shown in Scheme 4.7, this reaction indeed delivered the desired 1,5-diene product bearing an all-carbon quaternary center (**4.24**) with high a level of enantiomeric purity; however, a significant amount of 1,3-diene **4.25** was generated as well.

### Scheme 4.7



It is well documented that under Pd catalysis, 1,3-dienes can be synthesized from tertiary allylic carbonates through the  $\beta$ -H elimination of allyl-Pd intermediates (path a, Scheme 8).<sup>23</sup> In a complementary fashion, after the transmetallation of allylB(pin) onto Pd(II) and formation of complex bis( $\eta^1$ -allyl)palladium **4.V**, a metallo-ene-reaction can cause intramolecular H-abstraction and deliver the 1,3-diene, as well as propene. In fact, this transformation has been utilized to accelerate the Pd-catalyzed transformation of allylic electrophiles to 1,3-dienes.<sup>24</sup>

**Scheme 4.8**



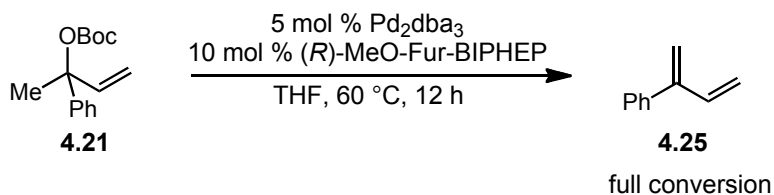
To obtain more information about side product formation, a control experiment was conducted, in which allylB(pin) was removed from the reaction. After the usual reaction period (12 hours), the tertiary allylic carbonate substrate was found to be completely converted to the 1,3-diene **4.25** (Scheme 4.9). This observation suggests that

<sup>23</sup> For similar observations: (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301. (c) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **2007**, *119*, 5956.

<sup>24</sup> Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151.

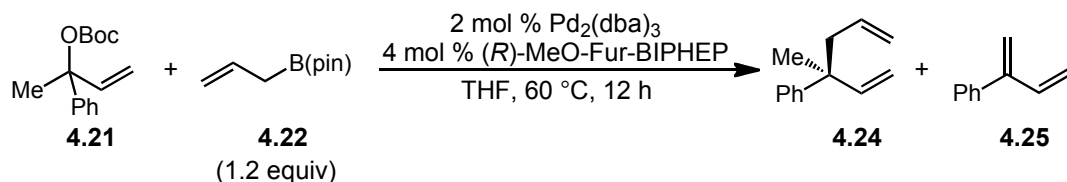
path a (Scheme 4.8) is likely responsible for generating the side product, but does not rule out the possibility of path b.

#### Scheme 4.9



With evidence that  $\beta$ -H elimination of complex **4.IV** (or related) contributes to the formation of **4.25**, we envisioned that the reaction efficiency could be improved by accelerating the transmetallation between **4.IV** and allylB(pin). Base additives known to speed up transmetallation of organoboronates in Suzuki-Miyaura reactions, such as  $\text{Cs}_2\text{CO}_3$  and  $\text{CsF}$ , were examined (Table 4.2). In a concentration dependent manner, the 1,5-diene/1,3-diene ratio was significantly improved with the presence of bases. With 10 equivalents of  $\text{CsF}$ , the desired **4.24** was the predominant product, isolated in 77% yield and 95:5 er.

**Table 4.2 Base Additive Evaluation**



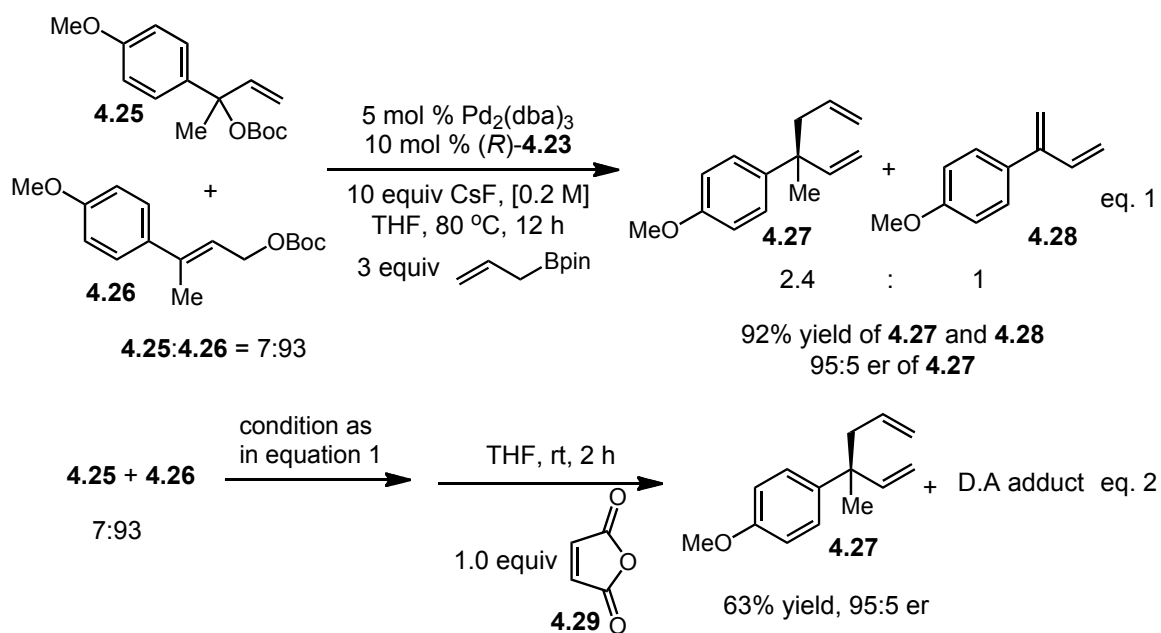
entry	variations of condition	4.24:4.25	yield <sup>a</sup>	er of 4.24
1	10 mol % catalyst	1:1	38%	96:4
2	10 mol % catalyst, 1.2 equiv $\text{Cs}_2\text{CO}_3$	2:1	90%	96:4
3	5 mol % catalyst, 1.2 equiv CsF	5:1	79%	96:4
4	3 equiv CsF	9:1	82%	95:5
5	10 equiv CsF	20:1	77%	95:5

<sup>a</sup> Isolated yield of purified products. 1,5- and 1,3-dienes were inseparable by chromatography, and the yield refers to the mixture.

With improved reaction conditions, a panel of allylic carbonates was synthesized and utilized to study the scope of this transformation. The optimal conditions for substrate **4.21** (entry 5, Table 4.2), however, do not reflect the best conditions for the rest of the substrates. In fact, a number of substrates suffer from relatively low selectivity to the desired 1,5-dienes, even after conditions were refined for each substrate by carefully tuning temperature, amount of base, equivalents of allylB(pin) and reaction time. The 1,5-dienes could be obtained in modest yields but are always mixed with the 1,3-dienes because the two compounds are inseparable by silica gel chromatography. Efforts were therefore taken to remove side products from reaction mixtures or further minimize their formation.

A promising strategy would be to treat the reaction mixture with a reagent which would selectively react with 1,3-dienes. Importantly, the product of such a transformation should be easily removed from the mixture, by either chromatography or reduced pressure. Utilizing activated dienophiles such as maleic anhydride, We envisioned that the Diels-Alder reaction could deliver this desired results. Such a reaction is expected to provide polar [4+2] adducts which would be easily separated with silica gel chromatography. An example of this method is given in Scheme 4.10. Under the standard conditions, a mixture of allylic carbonates **4.25** and **4.26** was converted to both 1,5-diene **4.27** and 1,3-diene **4.28** in 2.5 to 1 ratio, which could only be isolated as a mixture. When the reaction was treated with 1 equivalent of maleic anhydride at room temperature for 2 hours before work up, pure **4.27** was isolated as a single product after chromatography purification (equation 2).

**Scheme 4.10**





**B. Accelerating Transmetallation.** Although the Diels-Alder-trap works effectively, it was considered that accelerating transmetallation would potentially diminish by-product formation and result in higher yields. Therefore, two strategies were employed to achieve faster transmetallation:

*1. Replace allylB(pin) with more reactive allylmagnesiums.* As discussed in previous chapter, due to the strong electron donation from the oxygen lone pairs of pinacol, allylB(pin) is relatively inert towards basic activation. In the sterically congested environment in **4.IV**, transmetallation is relatively inefficient. In an attempt to overcome this, more reactive allylmagnesium bromide was employed. Unfortunately, preliminary study of this reagent in Pd-catalyzed allyl-allyl coupling resulted in the decomposition of starting materials.

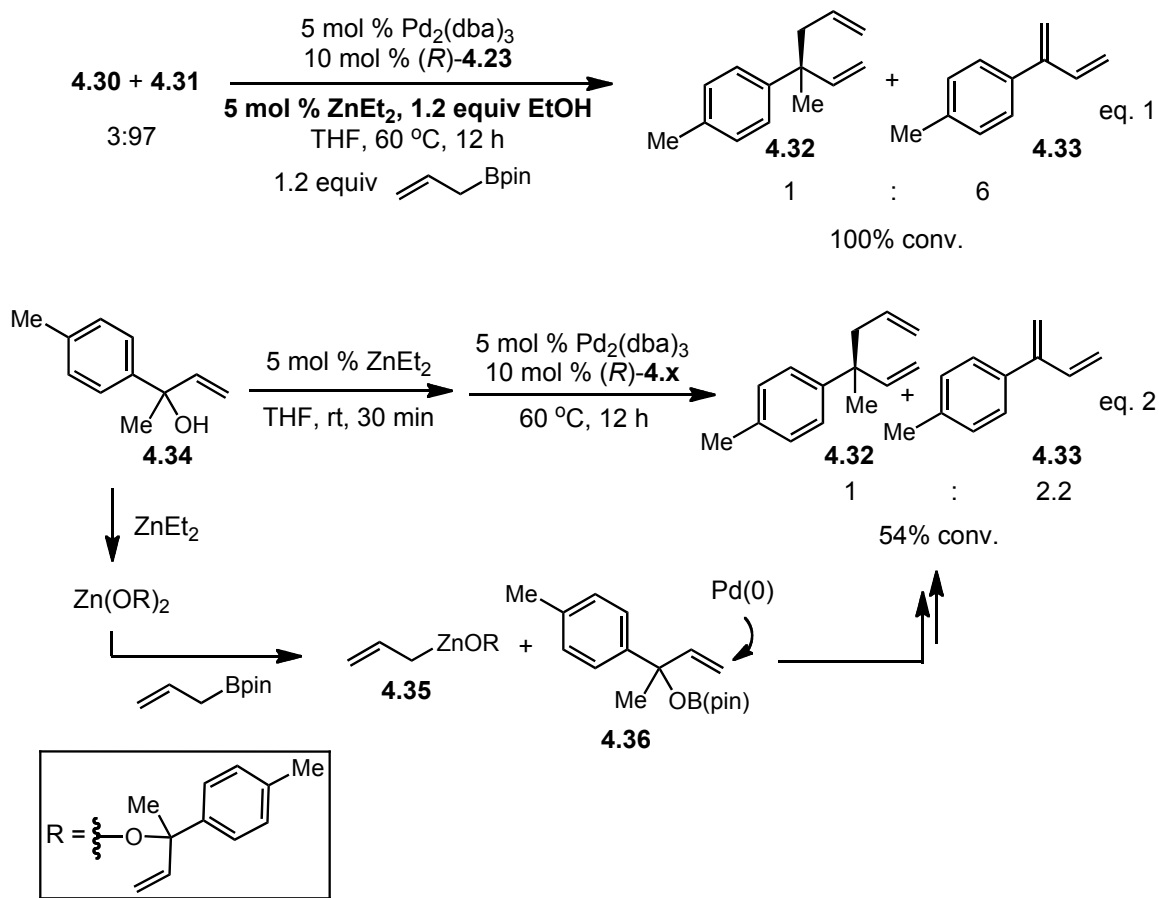
A recent study by Fandrick disclosed a novel strategy to activate allylic boronates in the allylation of ketones,<sup>25</sup> in which more reactive allylzinc reagents are generated *in situ* through a key allylborate-zinc alkoxide exchange path. Inspired by this work, we anticipated that transmetallation in allyl-allyl coupling could also benefit from the *in situ* formation of more reactive allylzinc species. As depicted in equation 1 (Scheme 4.11), a catalytic amount of ZnEt<sub>2</sub> was added to the reaction, along with ethanol, in order to generate a zinc alkoxide. Under these conditions, the reaction achieved full conversion; however, the product selectivity was significantly diminished. Since its impact on allyl-allyl coupling is not clear, ethanol was removed from the reaction. We anticipated that a zinc alkoxide could be generated directly between allylic alcohol **4.34** and ZnEt<sub>2</sub>, which

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<sup>25</sup> Fandrick, K. R.; Fandrick, D. R.; Gao, J. J.; Reeves, J. T.; Tan, T.; Li, Wen.; Song, J. J.; Lu, B.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 3748.

could also convert the hydroxyl group on **4.34** to a better leaving group in **4.36** upon zinc-boron transmetallation (equation 2, Scheme 4.11). As depicted, the reaction suffered from low conversion and poor 1,5/1,3-diene selectivity, although the expected double activation appeared to occur.

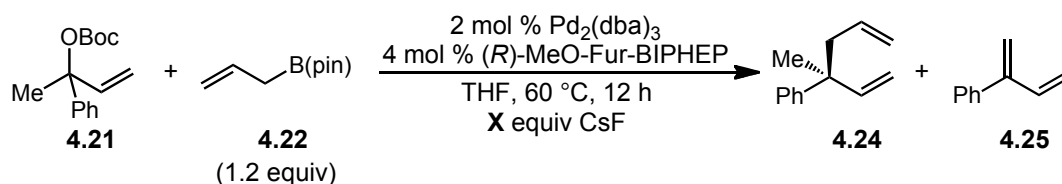
### Scheme 4.11



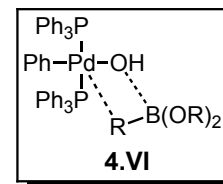
2. *Employ additives to facilitate transmetallation.* Water is a commonly used co-solvent in palladium-catalyzed cross-couplings, the role of which is not fully understood. Earlier optimization avoided the use of water due to the potential of generating allylic

alcohols through outer-sphere attack of water on  $\pi$ -allylpalladium complexes. Recent discoveries, however, suggested Pd(II)-OH as a key intermediate for the transmetalation of organoborates and boronic acids in cross-couplings, possibly proceeding through complex **4.VI** (Table 4.3).<sup>26</sup> Therefore, aqueous solvent systems were examined in the allyl-allyl coupling and found to effectively minimize the formation of 1,3-dienes (Table 4.3). Optimal conditions were found to involve CsF (3 equiv) and employ 10:1 THF-H<sub>2</sub>O as the solvent system. In this case, the allyl-allyl coupling product was obtained in excellent yield and high optical purity as a single regioisomer (entry 5).

**Table 4.3 Utilizing Water as Co-Solvent to Improve Reaction**



entry	THF:H <sub>2</sub> O	X	4.24:4.25	%yield <sup>a</sup>	er of 4.24
1	10:1	none	20:1	90	96:4
2	10:1	1.2	25:1	86	96:4
3	20:1	1.2	20:1	84	96:4
4	5:1	1.2	33:1	84	96:4
<b>5</b>	<b>10:1</b>	<b>3</b>	<b>50:1</b>	<b>90</b>	<b>96:4</b>

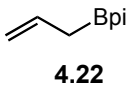
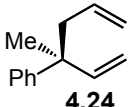
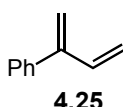
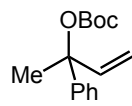
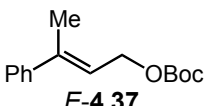
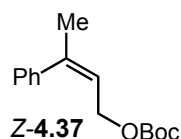


<sup>a</sup> Isolated yield of purified products. 1,5- and 1,3-dienes were inseparable by chromatography, and the yield refers to the mixture.

<sup>26</sup> (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. (b) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (c) Suzuki, Y.; Osakada, K. *Organometallics* **2006**, *25*, 3251.

**C. Substrate Scope of All-Carbon Quaternary Center Construction through Pd-Catalyzed Allyl-Allyl Cross-Coupling.** To examine the scope of this transformation, geometric and regioisomers were first studied. As shown in Table 4.4, *E* and *Z* primary carbonates (*E*-**4.37** and *Z*-**4.37**) deliver the same allyl-allyl coupling product **4.24** in comparable yields and selectivity to that starting with the racemic tertiary carbonate **4.22**. This observation suggests that fast  $\pi$ - $\sigma$ - $\pi$  isomerization of the  $\eta^3$ -pseudoprenyl-palladium complexes (of **4.I** and **4.III**, Scheme 4.4) allows for complete equilibration of the complexes and ultimately deliver the same reaction product.

**Table 4.4 Effect of Electrophile Geometry**

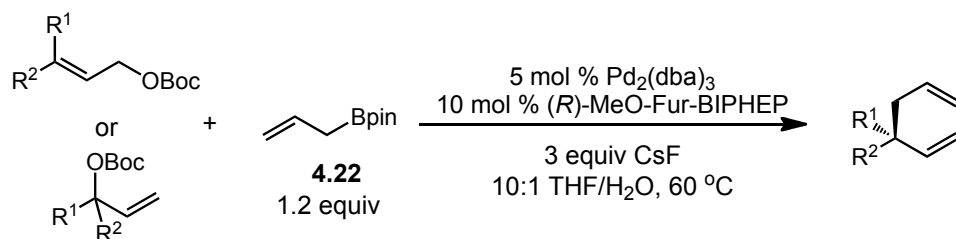
substrate +  <b>4.22</b> 1.2 equiv <div> <math>\xrightarrow[10:1 \text{ THF/H}_2\text{O}, 60^\circ\text{C}]{5 \text{ mol } \% \text{ Pd}_2(\text{dba})_3, 10 \text{ mol } \% (R)\text{-MeO-Fur-BIPHEP}, 3 \text{ equiv CsF}}</math> </div>			
 <b>4.24</b> +  <b>4.25</b>			
substrate	<b>4.24 : 4.25</b>	%yield	er
 <b>4.21</b>	>20:1	90	96:4
 <i>E</i> - <b>4.37</b>	>20:1	86	96:4
 <i>Z</i> - <b>4.37</b>	11:1	80	96:4

Taking advantage of rapid  $\pi$ - $\sigma$ - $\pi$  isomerization, not only the easily prepared racemic internal tertiary allylic carbonates can be employed as substrates, their

regioisomers (terminal carbonates) can also serve as suitable substrates and deliver the same allyl-allyl coupling products in similar selectivity and yields. This is an attractive practical feature of this transformation due to the difficulty of synthesizing isomerically pure starting materials: some of the tertiary allylic carbonates, synthesized through the vinyl addition to ketones followed by carbonate protection, isomerize during SiO<sub>2</sub> chromatography, resulting in mixtures of isomers. When such isomerization occurs, the mixtures can be directly employed as substrates.

As shown in Table 4.5, a range of allylic carbonates participate in the Pd-catalyzed allyl-allyl coupling and afford 1,5-dienes bearing all carbon quaternary centers in excellent enantiopurity. A good level of substitutions was tolerated. Oxygenated substrates reacted smoothly and delivered the desired products in good yields and selectivity (entries 5 and 6). Significantly, halogen-substituted aromatic substrates are converted to the corresponding 1,5-dienes in high efficiency, without any carbon-halogen bond insertion products observed (entries 1, 2 and 4). It is noteworthy that aromatic rings bearing *ortho*-substitution are also well tolerated (entry 4). Allylic carbonates bearing heterocycles are also suitable substrates for this coupling. Notably, the 2-pyridal compound **4.42** displays excellent reactivity under anhydrous conditions to furnish **4.48** in high levels of selectivity.

**Table 4.5 Aryl-Methyl Substrates**

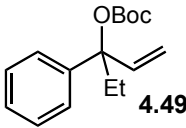
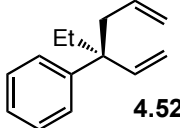
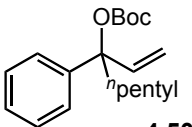
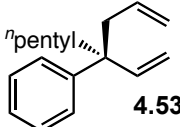
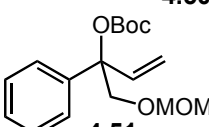
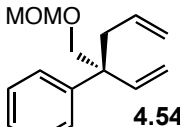


entry	substrate	product	%yield <sup>a</sup> (pdt:elim)	er
1	 <b>4.38</b>	 <b>4.43</b>	90(20:1)	95:5
2 <sup>b</sup>	 <b>4.39</b>	 <b>4.44</b>	70(>20:1)	95:5
3	 <b>4.30</b>	 <b>4.32</b>	76(17:1)	96:4
4 <sup>d</sup>	 <b>4.40</b>	 <b>4.45</b>	96(4:1)	92:8
5 <sup>c</sup>	 <b>4.26</b>	 <b>4.27</b>	83(12:1)	94:6
6 <sup>b,c</sup>	 <b>4.41</b>	 <b>4.47</b>	94(6:1)	96:4
7 <sup>e</sup>	 <b>4.42</b>	 <b>4.48</b>	81(>20:1)	95:5

<sup>a</sup> Isolated yield of purified products. 1,5- and 1,3-dienes were inseparable by chromatography, and the yield refers to the mixture. <sup>b</sup> Substrate was a mixtures of branch and linear allylic carbonates. <sup>c</sup> Reaction was run at 80 °C. <sup>d</sup> 10 Equiv CsF and 3 equiv allylB(pin) in 5:1 THF-H<sub>2</sub>O. <sup>e</sup> Reaction in anhydrous THF.

In addition to methylketone derived substrates as depicted in Table 4.5, substrates bearing longer aliphatic chains (**4.49** and **4.50**) are also converted to corresponding 1,5-diene products in good yields and with high enantioselectivity, albeit with increased formation of 1,3-diene by-products when compared to the methyl analogues (Table 4.6). The reaction also tolerates MOM protected alcohols, which deliver the expected diene product as a single compound, although with slightly lower enantioselectivity.

**Table 4.6<sup>a</sup> Phenyl-Alkyl Substrates**

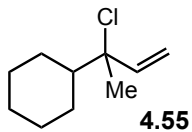
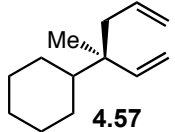
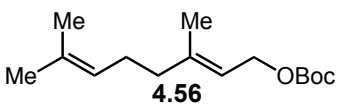
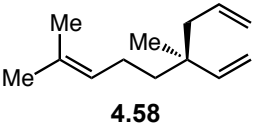
entry	substrate	product	%yield <sup>b</sup> (pdt:elim)	er
1 <sup>c</sup>	 <b>4.49</b>	 <b>4.52</b>	97(6:1)	94:6
2 <sup>c</sup>	 <b>4.50</b>	 <b>4.53</b>	78(6:1)	95:5
3 <sup>d</sup>	 <b>4.51</b>	 <b>4.54</b>	58(>20:1)	90:10

<sup>a</sup> General reaction condition is consistent with Table 4.5. <sup>b</sup> Isolated yield of purified products. 1,5- and 1,3-dienes were inseparable by chromatography, and the yield refers to the mixture. <sup>c</sup> Reaction was run at 80 °C. <sup>d</sup> Reaction in anhydrous THF.

To test if the effective prochiral face selection requires one of the substituents to be aromatic, substrates **4.55** and **4.56** were examined. Due to the difficulties in preparing the carbonate derivative of **4.55**, the chlorides were employed instead, which proved to be suitable starting material for allyl-allyl as well. To our delight, high levels of enantiocontrol were observed when the two enantiotopic groups on the substrates bear a

significant difference in size (entry 1, Table 4.7). When the variation is small, however, (methyl vs methylene in **4.58**), diminished enantioselectivity was observed. In both cases, due to the presence of more  $\beta$ -hydrogens, 1,3-diene formation is more prevalent than with aromatic substrates.

**Table 4.7<sup>a</sup> Alkyl-Alkyl Substrates**

entry	substrate	product	%yield <sup>b</sup> (pdt:elim)	er
1 <sup>c,d,e</sup>	 <b>4.55</b>	 <b>4.57</b>	48(8:1)	97:3
2 <sup>f</sup>	 <b>4.56</b>	 <b>4.58</b>	96(4:1)	76:24

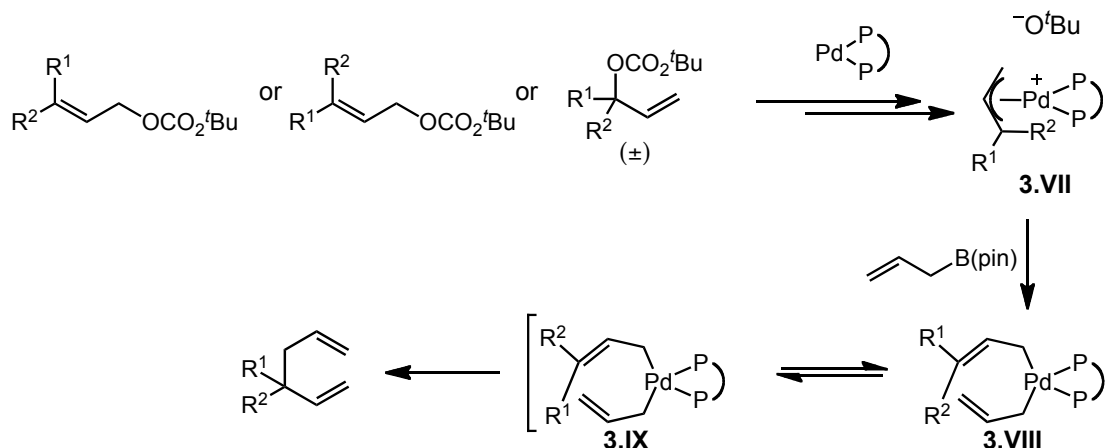
<sup>a</sup> General reaction condition is consistent with Table 4.5. <sup>b</sup> Isolated yield of purified products. 1,5- and 1,3-dienes were inseparable by chromatography, and the yield refers to the mixture. <sup>c</sup> Reaction time was 36 h. <sup>d</sup> Reaction in anhydrous THF. <sup>e</sup> A mixture of branch and linear allylic chlorides are used as substrate. <sup>f</sup> 10 Equiv CsF and 3 equiv allylB(pin) in 5:1 THF-H<sub>2</sub>O.

**D. Proposed Mechanism and A Model for the Stereocontrol in Enantioselective Construction of All-Carbon Quaternary Centers through Allyl-Allyl Coupling.** As described in previous sections, not only the racemic tertiary internal allylic carbonates but also their regioisomers can serve as interchangeable substrates in quaternary center construction. In analogy to the allyl-allyl cross-coupling described in Chapter III, we proposed that, subsequent to transmetallation between allylB(pin) and allylpalladium complex **3.VII**, the bis(allyl)palladium complexes (**3.VIII** and **3.IX**) are



able to undergo rapid isomerization prior to 3,3'-reductive elimination, which is the stereo-determining step. (Scheme 4.12)

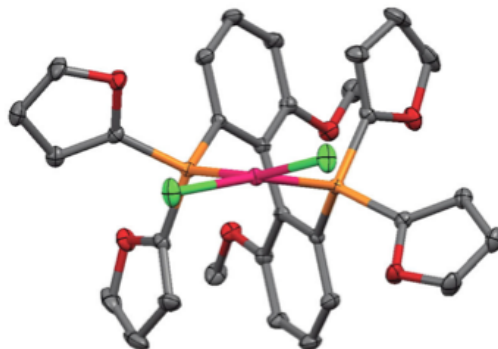
**Scheme 4.12**



In order to gain a sense of stereinduction in the allyl-allyl cross-coupling reactions, a crystal structure of (R)-MeO-Fur-BIPHEP (**4.23**) complexed to  $\text{PdCl}_2$  was determined by graduate student Michael Ardolino (Figure 4.1).<sup>27</sup> The structure indicates that the ligand-metal complex forms a seven-membered metallacycle. The furyl rings adopt pseudoaxial and pseudoequatorial positions on the seven-membered ring. The pseudoequatorial furyl rings have significant effects on the Pd square plane in a manner that causes the chlorine atoms to cant above or below the plane, and this is an important feature with respect to stereinduction in allyl-allyl couplings.

<sup>27</sup> Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

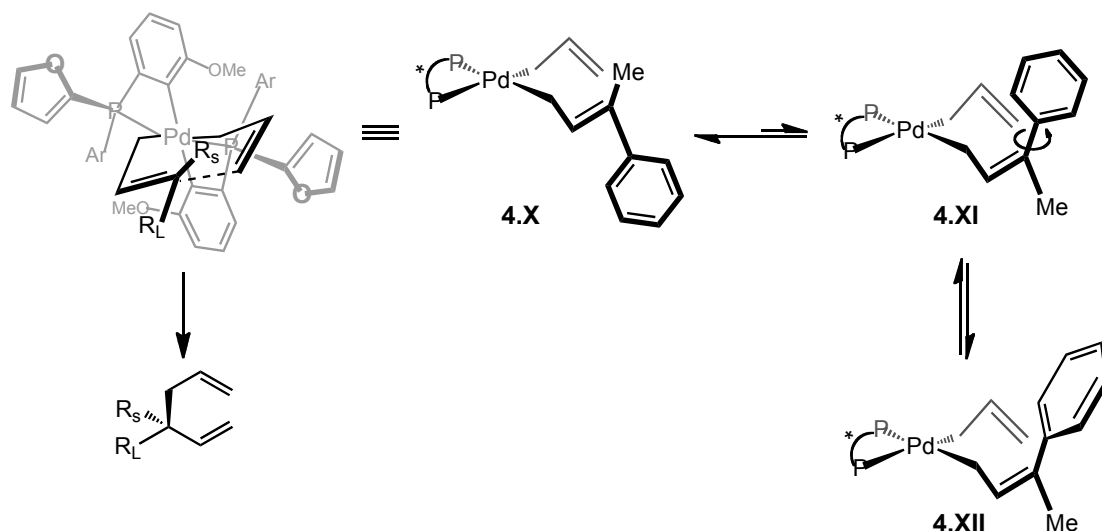
**Figure 4.1: Crystal Structure of [(*R*)-MeO-Fur-BIPHEP]PdCl<sub>2</sub>.**



Based on the crystal structure shown in Figure 4.1 and according to the computational studies by Echavarren, which suggested that such reactions occur through chair-like transition structures,<sup>28</sup> a favored reaction path is depicted in Scheme 4.13. In this model, the  $\eta^1$ -allyl ligands are each canted in a manner that minimizes interaction with the pseudoequatorial furyl rings of the ligand and they are placed in a pseudo-chair conformation. The 1,1-disubstituted allyl (pseudo-prenyl) ligand adopts the *E* configuration in order to minimize A(1,3) strain. When the large group is phenyl, a carbon-carbon single bond rotation could lower the A(1,3) strain by placing the aromatic ring orthogonal (as in **4.XII**) instead of in conjugation with the alkene moiety (as in **4.XI**), therefore **4.XII** might be favored. However, this complex (**4.XII**) is more likely be the least productive one because the phenyl group would shield the alkene from interacting with the second allyl ligand thereby preventing the formation of a C3-C3' bond. Therefore **4.X** is more favored and leads to high enantiomeric induction.

<sup>28</sup> Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, 8, 3620.

**Scheme 4.13**

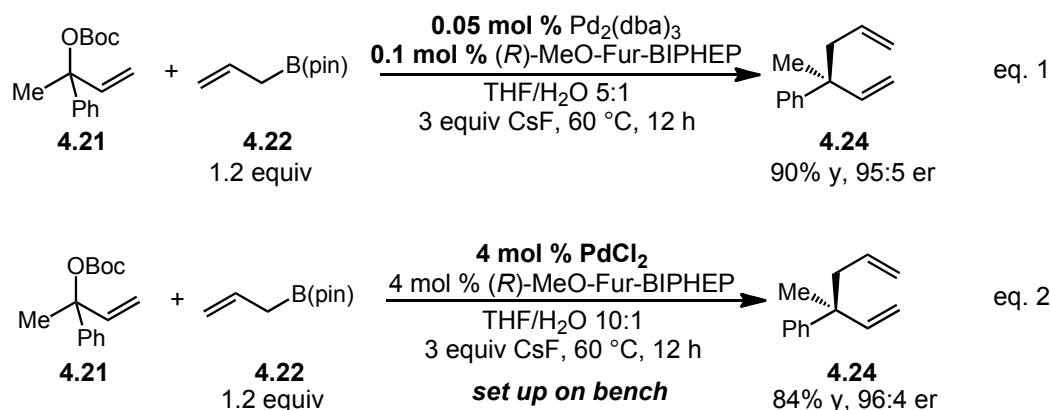


#### **E. Utility and Application of Pd-Catalyzed Quaternary Center Formation.**

Pd-catalyzed allyl-allyl cross-coupling has proven to be a versatile method for the creation of all-carbon quaternary centers with high levels of enantiocontrol. Further elaboration of these coupling products would furnish complex molecules bearing quaternary carbon centers. Before displaying the representative utilities of these compounds, as given in Scheme 4.14 the allyl-allyl coupling conditions can be modified so that they are more applicable for large-scale synthesis. After optimization, it was found that with only 0.1 mol % catalyst loading (0.1 mol % 'Pd'), full conversion is achieved within 12 hours (equation 1, Scheme 4.14), delivering the 1,5-diene product in comparable yield and selectivity to that of higher catalyst loading (e.g entry 5 Table 4.3). Importantly, air-stable  $\text{PdCl}_2$  was also found to be suitable palladium precursor, which

allows the reaction to be set up on bench top without the assistance of a dry-box (equation 2).

**Scheme 4.14**



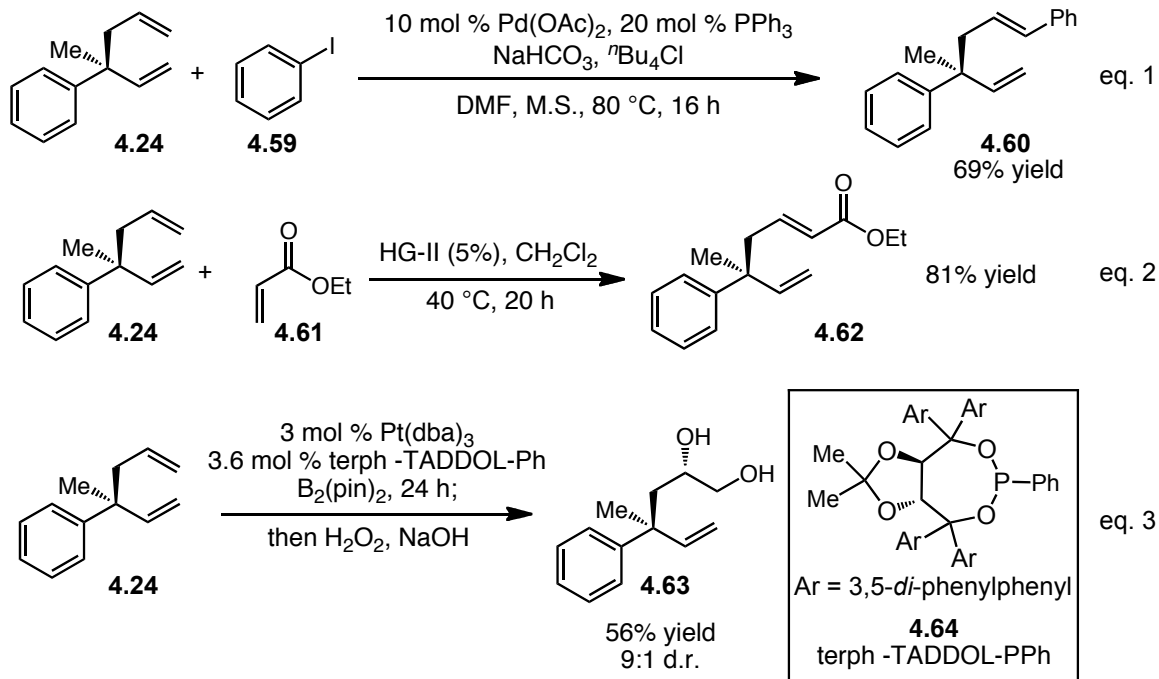
With the efficient and practical means to synthesize 1,5-dienes bearing all-carbon quaternary centers, it is important to selectively functionalize one of the olefins, especially for target-directed synthesis. As shown in equation 1, Scheme 4.15, a regioselective Heck reaction<sup>29</sup> was accomplished, where the sterically less encumbered alkene is selectively transformed. The high regioselection likely results from increased torsional strain that would penalize the carbon-metal bond formation through the more hindered alkene. Presumably due to the similar reasons, cross metathesis<sup>30</sup> (equation 2) and Pt-catalyzed diboration/oxidation<sup>31</sup> (equation 3) are both highly regioselective. Notably for the latter case, high levels of diastereoselectivity were also observed, which results from the enantiofacial selection derived from a chiral phosphonite ligand.

<sup>29</sup> Jeffery, T. *Tetrahedron Lett.* **1985**, 26, 2667. (b) Jeffery, T. *Tetrahedron* **1996**, 52, 10113.

<sup>30</sup> (a) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, 6, 3465. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussman, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, 122, 58.

<sup>31</sup> Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, 131, 13210.

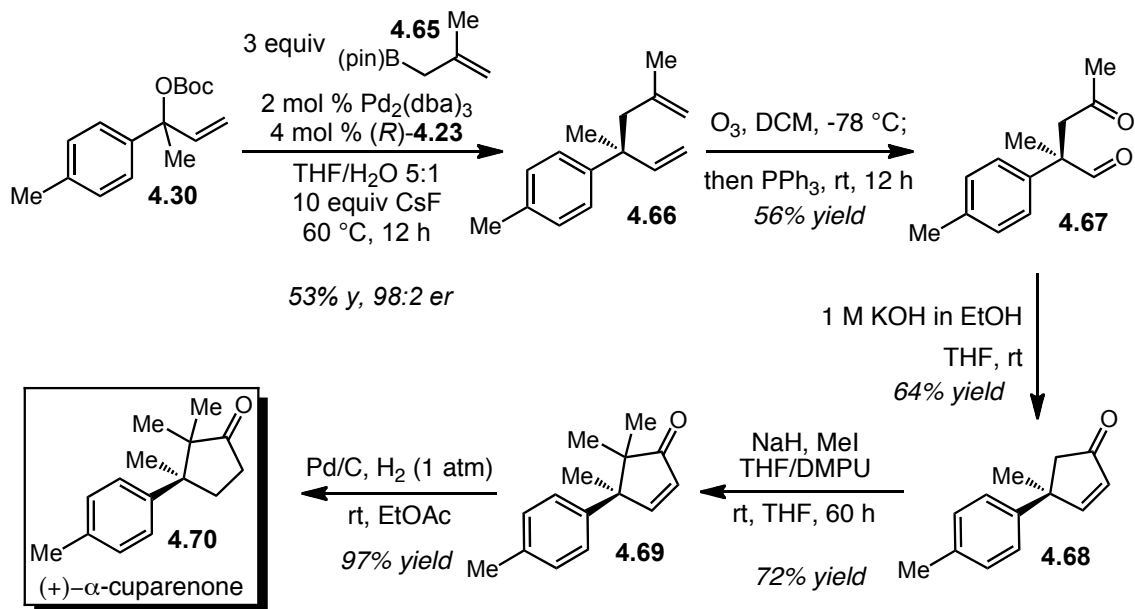
**Scheme 4.15**



As demonstrated in Chapter III,  $\beta$ -substituted allylB(pin) such as **4.65** also performs well as a coupling partner in allylic allylations. As demonstrated in Scheme 4.16, **4.65** can couple with allylic carbonate substrates with excellent enantiocontrol. Importantly, the coupling product (**4.67**) is a useful precursor for the construction of cyclopentenones bearing all-carbon quaternary centers. Upon ozonolysis, the resulting ketoaldehyde was readily converted to cyclopentenone **4.69** through intramolecular aldol condensation. Subsequent methylation and hydrogenation as reported by Myers,<sup>32</sup> delivered the natural product, presenting the shortest catalytic enantioselective synthesis of this molecule.

<sup>32</sup> Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541.

**Scheme 4.16**



#### IV. CONCLUSION

The Pd-catalyzed branch- and enantioselective allyl-allyl cross-coupling has been extended to the construction of synthetically more demanding, challenging all-carbon quaternary centers. Due to the fact that the rapid  $\pi$ - $\sigma$ - $\pi$  isomerization of allylpalladium likely is involved in the catalytic cycle, regio- and geometric isomers of allylic alcohols serve as interchangeable substrates, presenting a practical feature of this method. Regioselective functionalizations of the 1,5-diene products have also been demonstrated. The total synthesis of natural product (+)- $\alpha$ -cuparenone has been conducted, presenting the shortest catalytic enantioselective synthesis to date.

## V. EXPERIMENTAL PROCEDURES

### A. General Information

$^1\text{H}$  NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz) or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the reference ( $\text{CDCl}_3$ : 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and assignment.  $^{13}\text{C}$  NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Gemini-500 (125 MHz) or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the reference ( $\text{CDCl}_3$ : 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer,  $\nu_{\text{max}}$   $\text{cm}^{-1}$ . Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectra (ESI) were obtained at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed through the use of forced flow (flash chromatography) on silica gel ( $\text{SiO}_2$ , 230 $\times$ 450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25  $\mu\text{m}$  silica gel plates purchased from Silicycle. Visualization was performed through the use of ultraviolet light (254 nm) or potassium permanganate ( $\text{KMnO}_4$ ) in water. Analytical chiral gas-liquid chromatography (GC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco  $\beta$ -Dex 120 column or an Agilent Technologies 6850 equipped with a split mode capillary

injection system, a flame ionization detector, and a Supelco Chiraldex G-TA with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar SFC equipped with a Waters 2998 photodiode array detector and an analytical-2-prep column oven with methanol as the modifier. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1120 compact chromatograph equipped with gradient pump and variable wavelength detector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. X-Ray crystallography was performed on a Bruker Kappa Apex Duo fully automated single crystal diffractometer, duo wavelength system with high brightness copper source, and anomalous dispersion was used.

All reactions were conducted in oven- or flame-dried glasswares under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) was purified through the use of a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Tris(dibenzylideneacetone) dipalladium(0) [Pd<sub>2</sub>(dba)<sub>3</sub>] was purchased from Strem Chemicals, Inc. (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl [(*R*)-MeO-Fur-BIPHEP] was purchased from Strem Chemicals, Inc. or Aldrich, or generously donated from Solvas. Allylboronic acid pinacol ester [allylB(pin)] was generously donated by Frontier Scientific, Inc. MethallylB(pin) was synthesized as described in the literature.<sup>33</sup> All other reagents were purchased from either Fisher or Aldrich and used without further purification.

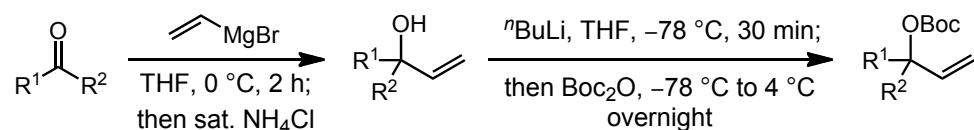
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<sup>33</sup> Zhang, P.; Brozek, L. B.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.



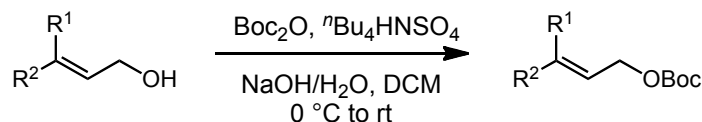
## B. Experimental Procedures

### 1. Preparation and Characterization of Allylic Carbonates



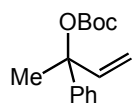
**Representative Procedure A:**<sup>33</sup> To a flame-dried round-bottom flask equipped with a stir bar was added 1.0 M vinylmagnesium bromide in THF (15.0 mL, 15.0 mmol) and THF (10 mL). The solution was cooled to  $0\text{ }^\circ\text{C}$  and acetophenone (1.20 g, 10.0 mmol) in THF (10 mL) was added dropwise *via* cannula. The reaction was allowed to stir at  $0\text{ }^\circ\text{C}$  for 2 hours. The reaction was then quenched with sat.  $NH_4Cl$  (aq.), and extracted into diethyl ether three times. The combined organics were washed with brine, dried over  $Na_2SO_4$ , filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (15:1 hexanes/EtOAc) to afford 1.20 g (81% yield) of 2-phenylbut-3-en-2-ol as a light yellow oil.  $R_f = 0.26$  (3:1 hexanes/EtOAc, stain in  $KMnO_4$ ). To a separate flame-dried round-bottom flask equipped with stir bar was added 2-phenylbut-3-en-2-ol (1.20 g, 8.10 mmol) and THF (16.0 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$  (dry ice/acetone) followed by dropwise addition of *n*-butyllithium (3.55 mL, 8.51 mmol) in hexane (2.40 M). The reaction was allowed to stir for 30 minutes at  $-78\text{ }^\circ\text{C}$ , after which  $Boc_2O$  (2.29 g, 10.5 mmol) in THF (5.0 mL) was added dropwise *via* cannula. The reaction was allowed to warm to  $4\text{ }^\circ\text{C}$  in a cold room and stir overnight. The reaction was diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted into diethyl ether three times. The combined organics were washed with brine, dried over  $Na_2SO_4$ , filtered, and then concentrated *in vacuo*. The unpurified

reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 1.65 g (82% yield) of *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate as a light yellow oil.  $R_f = 0.39$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).



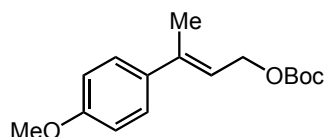
**Representative Procedure B:**<sup>33</sup> To a round-bottom flask equipped with a stir bar was added geraniol (1.54 g, 10.0 mmol) and methylene chloride (5 mL). The resulting solution was charged with  $\text{Boc}_2\text{O}$  (2.60 g, 12.0 mmol) and  $\text{Bu}_4\text{NHSO}_4$  (68.0 mg, 0.2 mmol). The solution was cooled to 0 °C and aqueous NaOH (5.4 mL, 30% solution in  $\text{H}_2\text{O}$ ) was added dropwise. The solution was allowed to stir overnight at room temperature. The reaction mixture was diluted with diethyl ether and water, and then extracted into diethyl ether three times. The combined organics were washed with 1M HCl, water, brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford 1.85 g (73% yield) of (*E*)-*tert*-butyl (3,7-dimethylocta-2,6-dien-1-yl) carbonate as a light yellow oil.  $R_f = 0.55$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of tert-butyl (2-phenylbut-3-en-2-yl) carbonate.** From commercially available acetophenone, procedure A was followed.



**tert-butyl (2-phenylbut-3-en-2-yl) carbonate (4.21).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.41 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.87 (3H, s,  $\text{OCCH}_3$ ), 5.27 (1H, dd,  $J = 10.5, 0.5$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.28 (1H, dd,  $J = 17.5, 0.5$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.34 (1H, dd,  $J = 17.5, 10.5$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.24-7.27 (1H, m, Ar-H), 7.32-7.35 (2H, m, Ar-H), 7.37-7.40 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.8, 27.8, 81.8, 83.8, 115.1, 125.1, 127.2, 128.2, 141.0, 143.7, 151.5; IR (neat): 2980.4 (w), 2943.7 (w), 1743.1 (s), 1448.4 (w), 1368.7 (m), 1276.6 (s), 1254.2 (s), 1150.0 (s), 1070.5 (m), 792.9 (m), 699.1 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{11}$  [M-OBoc]: calculated: 131.0681, found: 131.0859; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, flashed with 100:1 hexanes/EtOAc) to afford 1.65 g (82% yield) of a light yellow oil.  $R_f = 0.39$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of (*E*)-*tert*-butyl (3-(4-methoxyphenyl)but-2-en-1-yl) carbonate.** From commercially available 4'-methoxyacetophenone, procedure A was followed. *tert*-Butyl (2-(4-methoxyphenyl)but-3-en-2-yl) carbonate was originally formed, which was isomerized to the corresponding linear isomer upon silica gel chromatography.



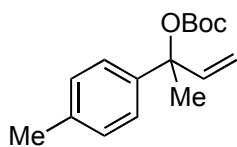
**(*E*)-*tert*-butyl**

**(3-(4-methoxyphenyl)but-2-en-1-yl)**

**carbonate (4.26).**

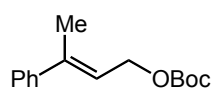
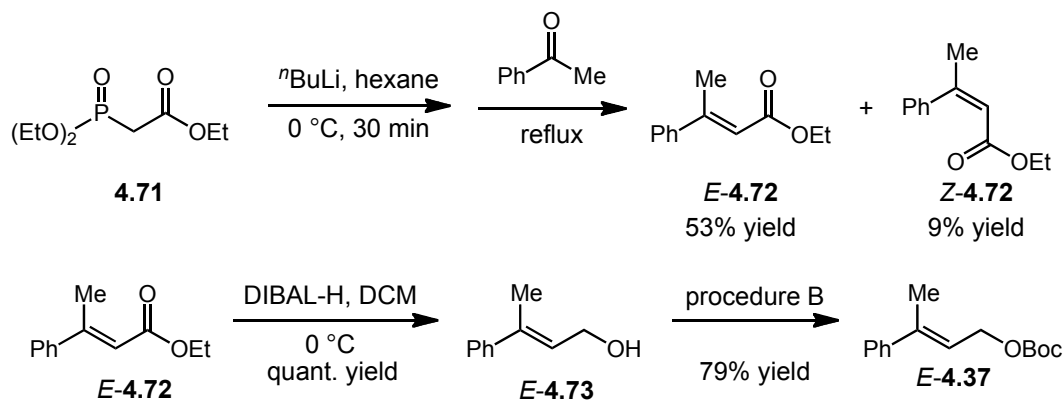
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.50 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.10 (3H, s, CH<sub>3</sub>C=CH), 3.81 (3H, s, OCH<sub>3</sub>), 4.77 (2H, d, *J* = 7.0 Hz, CH<sub>2</sub>OBoc), 5.85-5.88 (1H, m, ArMeC=CH), 6.84-6.87 (2H, m, Ar-H), 7.33-7.36 (2H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 16.2, 27.8, 55.2, 64.0, 82.0, 113.6, 119.4, 126.9, 134.9, 139.9, 153.6, 159.1; IR (neat): 2979.5 (w), 2934.4 (w), 2836.9 (w), 1734.7 (s), 1645.2 (m), 1711.7 (s), 1458.7 (w), 1368.4 (m), 1271.6 (s), 1243.5 (s), 1155.3 (s), 1083.4 (m), 825.1 (m), 792.6 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>11</sub>H<sub>13</sub>O [M-OBoc]: calculated: 161.0966, found: 161.0969; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 873 mg (75% yield) of a light yellow oil. R<sub>f</sub> = 0.42 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).

**Preparation of tert-butyl (2-(p-tolyl)but-3-en-2-yl) carbonate.** From commercially available 4'-methylacetophenone, procedure A was followed.



**tert-butyl (2-(p-tolyl)but-3-en-2-yl) carbonate (4.30).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.43 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.87 (3H, s,  $\text{OCCCH}_3$ ), 2.34 (3H, s, Ar- $\text{CH}_3$ ), 5.26 (1H, d,  $J = 11.0$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.28 (1H, d,  $J = 17.5$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.35 (1H, ddd,  $J = 17.5, 11.0, 0.5$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.16 (2H, d,  $J = 8.0$  Hz, Ar-H), 7.28 (2H, d,  $J = 8.0$  Hz, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.0, 25.7, 27.7, 81.6, 83.7, 114.8, 124.9, 128.9, 136.8, 140.7, 141.1, 151.5; IR (neat): 2979.9 (w), 2933.0 (w), 1743.0 (s), 1513.2 (w), 1455.9 (w), 1368.0 (m), 1274.9 (s), 1252.7 (s), 1122.0 (s), 1093.4 (s), 1073.1 (m), 850.6 (m), 791.2 (m), 533.4 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{11}\text{H}_{13}$  [M-OBoc]: calculated: 145.1017, found: 145.1023; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes:EtOAc) to afford 1.91 g (89% yield) of a light yellow oil.  $R_f = 0.49$  (8:1 hexanes:EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of (*E*)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate.** From allylic alcohol *E*-4.73, synthesized as shown below, procedure B was followed.



**(*E*)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate (*E*-4.37).**  $^1\text{H}$  NMR

(500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.51 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.31 (3H, d,  $J = 1.0$  Hz,

$\text{CH}_3\text{C}=\text{CH}$ ), 4.80 (2H, d,  $J = 7.0$  Hz,  $\text{C}=\text{CHCH}_2\text{OBoc}$ ), 5.93 (1H, tq,  $J = 7.0, 1.0$  Hz,  $\text{C}=\text{CHCH}_2$ ), 7.26-7.29 (1H, m, Ar-H), 7.32-7.35 (2H, m, Ar-H), 7.40-7.42 (2H, m, Ar-H);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.2, 27.7, 68.9, 82.0, 121.0, 125.8, 127.5, 128.2, 140.4,

142.5, 153.5; IR (neat): 2979.7 (w), 2939.9 (w), 1735.6 (s), 1445.2 (w), 1390.0 (m),

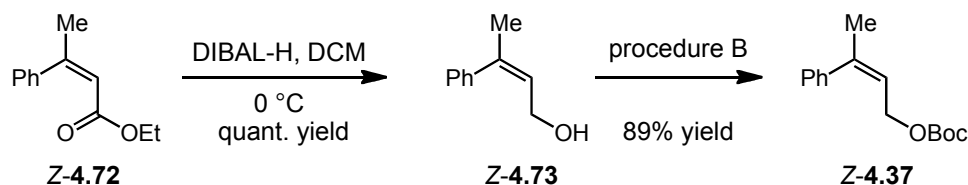
1333.2 (s), 1270.8 (s), 1156.6 (s), 1086.1 (m), 927.4 (w), 860.3 (m), 751.3 (m), 695.0 (m)

$\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{11}$  [M-OBoc]: calculated: 131.0861, found: 131.0866; The

unpurified reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford

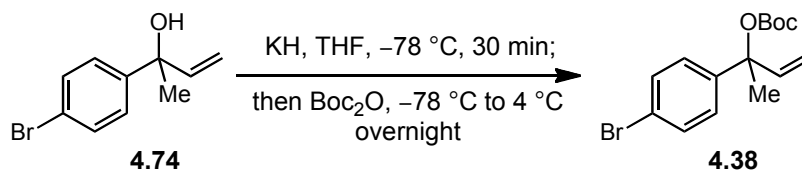
2.20 g (79% yield) of a light yellow oil.  $R_f = 0.71$  (3:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of (Z)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate.** From allylic alcohol Z-4.73, synthesized as shown below, procedure B was followed.



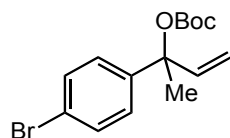
**(Z)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate (E-4.73).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.47 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.09-2.10 (3H, m,  $\text{CH}_3\text{C}=\text{CH}$ ), 4.50 (2H, dd,  $J = 7.0, 1.0$  Hz,  $\text{C}=\text{CHCH}_2\text{OBoc}$ ), 5.67-5.70 (1H, m,  $\text{C}=\text{CHCH}_2$ ), 7.17-7.19 (1H, m, Ar-H), 7.26-7.29 (2H, m, Ar-H), 7.32-7.36 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.4, 27.8, 64.7, 81.9, 120.9, 127.4, 127.7, 128.2, 140.3, 142.8, 153.5; IR (neat): 2978.5 (w), 2932.6 (w), 1736.8 (s), 1493.7 (w), 1444.1 (w), 1368.6 (m), 1273.4 (s), 1251.6 (s), 1159.1 (s), 1092.4 (m), 860.3 (m), 793.3 (m), 701.6 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{11}$  [M-OBoc]: calculated: 131.0861, found: 131.0864; The unpurified reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford 398 mg (89% yield) of a light yellow oil.  $R_f = 0.51$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of 2-(4-bromophenyl)but-3-en-2-yl tert-butyl carbonate.** From commercially available 4'-bromoacetophenone, procedure A was followed for the synthesis of allylic alcohol (**4.74**), which was converted to the carbonate as shown below.



**Procedure:** A flame-dried round-bottom flask was charged with KH (562.0 mg, 30 wt % in mineral oil, 4.2 mmol) and purged with N<sub>2</sub> three times. Dry hexane (5 mL) was added and the flask was gently swirled. Once the KH settled on the bottom of the flask, hexane was removed *via* cannula. This process was repeated twice, then THF (4.0 mL) was added to create a suspension. The suspension was transferred *via* cannula to another flame-dried round-bottom flask containing a solution of allylic alcohol (**S1**) (852.0 mg, 4.0 mmol) in THF (3.0 mL) at  $-78\text{ }^\circ\text{C}$ . The reaction was allowed to stir for 30 minutes at this temperature, followed by addition of Boc<sub>2</sub>O (1.13 g, 5.2 mmol) in THF (1.0 mL) *via* cannula. The reaction was allowed to warm to  $4\text{ }^\circ\text{C}$  in a cold room and stir overnight. The reaction was diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 1.10 g (84% yield) of a light yellow oil.  $R_f = 0.50$  (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).

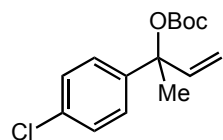




**2-(4-bromophenyl)but-3-en-2-yl *tert*-butyl carbonate (4.38).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.42 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.84 (3H, s,  $\text{OCCCH}_3$ ), 5.26-5.29 (2H, m,  $\text{CH}=\text{CH}_2$ ), 6.30 (1H, dd,  $J = 17.0, 11.0$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.26 (2H, ddd,  $J = 8.5, 2.5, 2.0$  Hz, Ar-H), 7.46 (2H, ddd,  $J = 8.5, 2.5, 2.0$  Hz, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.6, 27.7, 82.0, 83.2, 115.5, 121.3, 126.9, 131.3, 140.5, 142.9, 151.4; IR (neat): 2980.5 (w), 2935.2 (w), 1742.2 (s), 1488.1 (w), 1368.4 (m), 1280.2 (s), 1253.7 (s), 1153.1 (s), 1113.6 (m), 1090.9 (s), 1077.2 (s), 1008.2 (s), 926.3 (m), 820.9 (s), 720.2 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{10}\text{Br}$  [M-OBoc]: calculated: 208.9966, found: 208.9975.

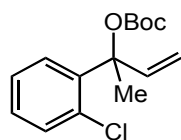
**Preparation of *tert*-butyl-(2-(4-chlorophenyl)but-3-en-2-yl)carbonate.** From commercially available 4'-chloroacetophenone, procedure A was followed.



***tert*-butyl-(2-(4-chlorophenyl)but-3-en-2-yl)carbonate (4.39).**  $^1\text{H}$

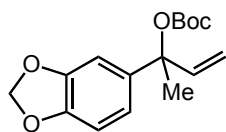
NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.42 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.85 (3H, s,  $\text{CCH}_3$ ), 5.25-5.29 (2H, m,  $\text{CH}=\text{CH}_2$ ), 6.30 (1H, dd,  $J = 17.4, 10.8$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.29-7.31 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.7, 27.8, 82.0, 83.2, 115.5, 126.6, 128.4, 133.1, 140.6, 142.3, 151.4; IR (neat): 2981.0 (w), 2004.2 (w), 1745.7 (s), 1492.0 (w), 1369.5 (m), 1284.6 (s), 1158.2 (s), 1013.2 (s), 827.7 (w), 421.7 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{10}\text{Cl}$  [M-OBoc]: calculated: 165.0471, found: 165.0464. The unpurified material was used for the subsequent coupling reaction without further purification.

**Preparation of *tert*-butyl-(2-(chlorophenyl)but-3-en-2-yl)carbonate.** From commercially available 2'-chloroacetophenone, procedure A was followed.



***tert*-butyl-(2-(chlorophenyl)but-3-en-2-yl)carbonate (4.40).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.43 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.95 (3H, s,  $\text{CCH}_3$ ), 5.23 (1H, d,  $J = 17.6$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.28 (1H, d,  $J = 10.9$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.49 (1H, dd,  $J = 17.6, 10.9$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.20-7.28 (m, 2H, Ar-H), 7.35-7.37 (m, 1H, Ar-H), 7.47-7.49 (m, 1H, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.8, 27.7, 81.9, 83.2, 115.4, 126.6, 127.8, 128.6, 131.6, 131.7, 139.9, 140.2, 151.4; IR (neat): 2981.4 (w), 2934.2 (w), 1741.4 (s), 1473.1 (w), 1369.2 (m), 1285.8 (s), 1256.3 (m), 1157.2 (s), 1134.2 (m), 1102.3 (m), 1038.8 (m), 926.9 (w), 791.6 (w), 755.5 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{23}\text{ClNO}_3$  [ $\text{M}+\text{NH}_4^+$ ]: calculated: 300.1367, found: 300.1371. The unpurified reaction mixture was purified on silica gel (hexanes to 32:1 hexanes/EtOAc) to afford a clear, colorless oil (1.40 g, 67% yield).  $R_f = 0.18$  (32:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

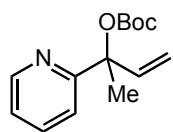
**Preparation of 2-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-yl-*tert*-butyl-carbonate.** From commercially available 3',4'-(methylenedioxy)acetophenone, procedure A was followed.



**2-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-yl-*tert*-butyl-carbonate**

**(4.41):**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.42 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.84 (3H, s,  $\text{CCH}_3$ ), 5.25 (1H, dd,  $J = 10.8, 0.7$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.27 (1H dd,  $J = 17.4, 0.7$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.95 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.30 (1H, dd,  $J = 17.4, 10.8$  Hz,  $\text{CCH}=\text{CH}_2$ ), 6.76 (1H, d,  $J = 8.1$  Hz, Ar-H), 6.85-6.89 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.7, 27.7, 81.7, 83.5, 101.0, 106.1, 107.8, 114.9, 118.4, 137.7, 141.0, 146.6, 147.6, 151.4; IR (neat): 2980.7 (w), 2932.1 (w), 1742.3 (s), 1486.7 (s), 1435.7 (m), 1393.9 (m), 1277.2 (s), 1241.5 (s), 1156.5 (s), 1094.5 (s), 1037.6 (s), 909.5 (m), 810.7 (m), 729.7 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{16}\text{H}_{21}\text{O}_5$   $[\text{M}+\text{H}]^+$ : calculated: 293.1389, found: 293.1375. The unpurified reaction mixture was purified on silica gel (9:1 hexanes/EtOAc) to afford a clear, pale-yellow oil (244 mg, 23% yield).  $R_f = 0.12$  (19:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

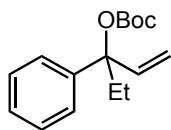
**Preparation of *tert*-butyl-(2-pyridin-2-yl)but-3-en-2-yl)carbonate.** From commercially available 2-acetylpyridine, procedure A was followed.



***tert*-butyl-(2-pyridin-2-yl)but-3-en-2-yl)carbonate (4.42).**  $^1\text{H}$  NMR

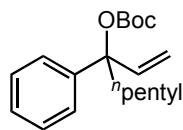
(500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.39 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.87 (3H, s,  $\text{CCH}_3$ ), 5.25 (1H, dd,  $J = 10.9, 0.7$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.31 (1H, dd,  $J = 17.6, 0.7$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.44 (1H, dd,  $J = 17.6, 10.9$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.12-7.15 (1H, m, Ar-H), 7.37-7.39 (1H, m, Ar-H), 7.62-7.65 (1H, m, Ar-H), 8.54-8.55 (1H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.0, 27.6, 81.9, 84.0, 115.0, 119.5, 122.0, 136.4, 140.1, 148.6, 151.5, 162.1; IR (neat): 2980.9 (w), 2936.2 (w), 1742.8 (s), 1588.8 (w), 1368.3 (m), 1278.0 (s), 1255.0 (s), 1156.7 (s), 1106.6 (s), 853.6 (m), 748.7 (m), 684.1 (m), 403.3 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{20}\text{NO}_3$   $[\text{M}+\text{H}]$ : calculated: 250.1443, found: 250.1440. The unpurified reaction mixture was purified on silica gel (9:1 hexanes/EtOAc) to afford a clear, pale-yellow oil (126 mg, 52% yield).  $R_f = 0.22$  (9:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of *tert*-butyl (3-phenylpent-1-en-3-yl) carbonate.** From commercially available propiophenone, procedure A was followed.



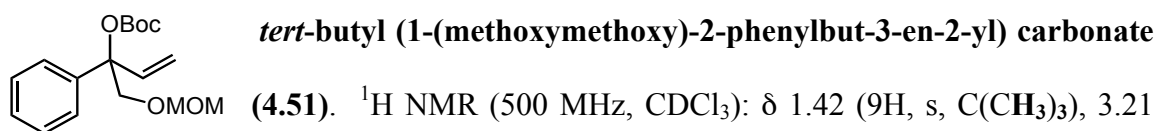
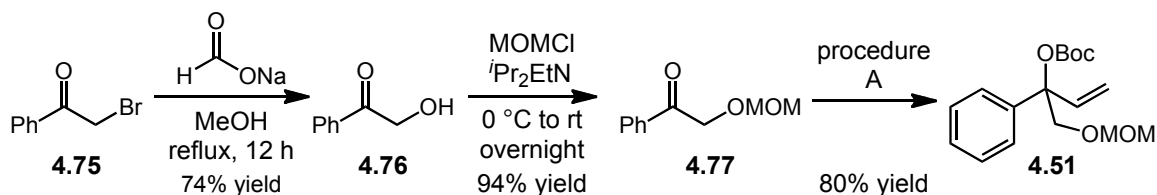
***tert*-butyl (3-phenylpent-1-en-3-yl) carbonate (4.49).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.82 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.42 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.27 (1H, dq,  $J = 14.0, 7.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}_3$ ), 2.33 (1H, dq,  $J = 14.0, 7.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}_3$ ), 5.29 (1H, dd,  $J = 11.0, 1.0$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.32 (1H, dd,  $J = 17.5, 1.0$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.22 (1H, dd,  $J = 17.5, 11.0$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.23-7.26 (1H, m, Ar-H), 7.31-7.38 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.7, 27.7, 30.9, 81.5, 85.9, 115.1, 125.5, 127.0, 128.0, 140.0, 142.6, 151.4; IR (neat): 3060.8 (w), 2978.5 (m), 2973.4 (w), 2881.6 (w), 1742.5 (s), 1640.1 (w), 1493.9 (w), 1448.3 (m), 1368.2 (m), 1269.4 (s), 1271.1 (s), 1152.7 (s), 1117.0 (m), 866.4 (s), 697.7 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{11}\text{H}_{13}$  [M-OBoc]: calculated: 145.1017, found: 145.1021; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 2.97 g (87% yield) of a light yellow oil.  $R_f = 0.46$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of *tert*-butyl (3-phenyloct-1-en-3-yl) carbonate.** From commercially available hexanophenone, procedure A was followed.



***tert*-butyl (3-phenyloct-1-en-3-yl) carbonate (4.50).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.84 (3H, t,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.14-1.30 (6H, m,  $(\text{CH}_2)_3\text{CH}_3$ ), 1.42 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.19-2.30 (2H, m,  $\text{CH}_2(\text{CH}_2)_3\text{CH}_3$ ), 5.27 (1H, dd,  $J = 11.0, 1.0$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.30 (1H, dd,  $J = 17.5, 1.0$  Hz,  $\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 6.23 (1H, ddd,  $J = 17.5, 11.0, 0.5$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.23-7.26 (1H, m, Ar-H), 7.31-7.38 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.0, 22.4, 22.9, 27.8, 31.9, 37.9, 81.6, 85.7, 114.9, 125.4, 127.0, 128.1, 140.4, 142.9, 151.4; IR (neat): 2957.2 (w), 2931.4 (w), 2870.6 (w), 1743.9 (s), 1448.4 (w), 1368.1 (m), 1271.1 (s), 1153.0 (s), 1123.9 (s), 910.9 (m), 790.2 (m), 697.8 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{19}$  [M-OBoc]: calculated: 187.1487, found: 187.1484; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 4.11 g (89% yield) of a light yellow oil.  $R_f = 0.56$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

**Preparation of *tert*-butyl (1-(methoxymethoxy)-2-phenylbut-3-en-2-yl) carbonate.** From ketone **4.77**, synthesized as shown below, procedure A was followed.



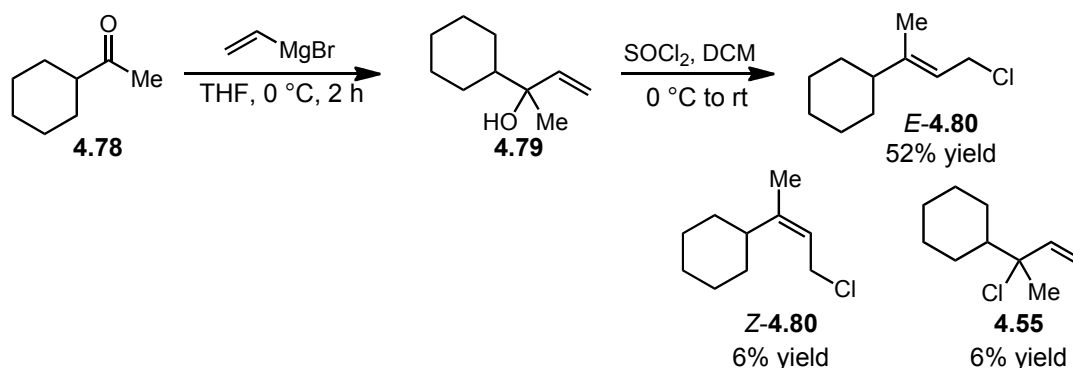
(3H, s, OCH<sub>3</sub>), 4.13 (1H, d, *J* = 10.0 Hz, CCH<sub>a</sub>H<sub>b</sub>O), 4.17 (1H, d, *J* = 10.0 Hz, CCH<sub>a</sub>H<sub>b</sub>O), 4.56 (1H, d, *J* = 6.5 Hz, OCH<sub>a</sub>H<sub>b</sub>O), 4.59 (1H, d, *J* = 6.5 Hz, OCH<sub>a</sub>H<sub>b</sub>O), 5.36 (1H, dd, *J* = 17.5, 0.5 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 5.40 (1H, dd, *J* = 11.0, 0.5 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 6.38 (1H, dd, *J* = 17.5, 11.0, Hz, CH=CH<sub>2</sub>), 7.26-7.29 (1H, m, Ar-H), 7.33-7.36 (4H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 27.7, 55.3, 71.4, 82.0, 84.2, 96.5, 116.9, 125.7, 127.5, 128.1, 137.7, 140.4, 151.3; IR (neat): 2979.7 (w), 2933.7 (w), 2886.8 (w), 2823.9 (w), 1743.8 (s), 1495.0 (w), 1449.2 (w), 1393.9 (m), 1270.9 (s), 1252.2 (s), 1147.8 (s), 1038.5 (s), 918.8 (m), 857.5 (m), 719.7 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>12</sub>H<sub>15</sub>O<sub>2</sub> [M-OBoc]: calculated: 191.1072, found: 191.1073; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 15:1 hexanes/EtOAc) to afford 2.35 g (80% yield) of a light yellow oil. *R*<sub>f</sub> = 0.30 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).



**Preparation of (E)-tert-butyl (3,7-dimethylocta-2,6-dien-1-yl) carbonate (4.56).** From commercially available geraniol, procedure B was followed. Spectral data is in accordance with literature.<sup>34</sup>

## 2. Preparation and Characterization of Allylic Chlorides

**Preparation of (4-chlorobut-2-en-2-yl)cyclohexane and (2-chlorobut-3-en-2-yl)cyclohexane.** From commercially available 1-cyclohexylethanone, procedure A was followed to synthesize allylic alcohol **4.79**, which was converted the chlorides as shown below.



**Procedure:**<sup>35</sup> To a flame-dried round-bottom flask under a  $\text{N}_2$  atmosphere was added  $\text{SOCl}_2$  (1.45 mL, 20.0 mmol) and  $\text{CH}_2\text{Cl}_2$  (8 mL) at room temperature. The resulting solution was cooled to  $0\text{ }^{\circ}\text{C}$ , and 2-cyclohexylbut-3-en-2-ol (**4.79**, 308 mg, 2.0 mmol) was added dropwise. The solution was stirred at  $0\text{ }^{\circ}\text{C}$  for 0.5 h, then allowed to warm to room temperature and stir for an additional 1.5 h. The solution was then cooled to  $0\text{ }^{\circ}\text{C}$  and ice-cold DI water was added to quench excess  $\text{SOCl}_2$ . The mixture was extracted with diethyl

<sup>34</sup> Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, 48, 7899.

<sup>35</sup> Penjišević, J.; Šukalović, V.; Andrić, D.; Kostić-Rajačić, S.; Šoškić, V.; and Roglić, G. *Arch. Pharm. Chem. Life Sci.* **2007**, 340, 456.

ether three times. The combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to afford 220 mg (64% yield) of a light brown oil. The unpurified reaction mixture was used without further purification.  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ ):  $\delta$  1.20-1.35 (m), 1.61 (s), 1.68-1.71 (m), 1.74-1.78 (m), 1.79-1.81(m), 4.11 (**A** & **B**, 2H, d,  $J = 8.0$  Hz,  $\text{CHCH}_2$ ), 5.13 (**C**, 1H, d,  $J = 10.8$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.26 (**C**, 1H, d,  $J = 17.3$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.34-5.41 (**B**, m, 1H,  $\text{C}=\text{CH}$ ), 5.40-5.45 (**A**, m,  $\text{C}=\text{CH}$ ), 6.01 (**C**, dd,  $J = 17.2, 10.7$  Hz,  $\text{CCH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.4, 19.8, 26.0, 26.2, 26.5, 30.9, 31.5, 41.3, 47.1, 118.4, 147.9; HRMS (ESI+) for  $\text{C}_{10}\text{H}_{17}$  [ $\text{M}-\text{Cl}$ ]: calculated: 137.1330, found: 137.1331.

**3. Representative Procedure for  $\text{Pd}_2(\text{dba})_3$ -Catalyzed Coupling (without water).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (3.6 mg, 0.004 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and THF (1.0 mL) in a dry-box under an argon atmosphere. The vial was capped and stirred for 5 minutes, then *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (49.6 mg, 0.20 mmol) was added, followed by allylboronic acid pinacol ester (40.4 mg, 0.24 mmol) and cesium fluoride (91.1 mg, 0.60 mmol). The vial was sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. The vial was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of silica gel and concentrated *in vacuo*. Analysis of the unpurified reaction mixture through the use of  $^1\text{H}$  NMR was used to determine the ratio of product to elimination product. Silica gel chromatography (pentane) afforded

27.4 mg (82% yield) of a colorless oil, with 7.3:1 allyl-allyl coupling product to elimination product.

#### **4. Representative Procedure for Pd<sub>2</sub>(dba)<sub>3</sub>-Catalyzed Coupling (with water).**

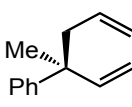
An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (3.6 mg, 0.004 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and 1.0 mL of THF in a dry-box under an argon atmosphere. The vial was capped and stirred for 5 minutes, then *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (49.6 mg, 0.20 mmol) was added, followed by allylboronic acid pinacol ester (40.4 mg, 0.24 mmol) and cesium fluoride (91.1 mg, 0.60 mol). The vial was sealed with a septum, removed from the dry-box, and then deoxygenated water (0.1 mL) was added by syringe under N<sub>2</sub> atmosphere. The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of MgSO<sub>4</sub> (top) and silica gel (bottom) and concentrated *in vacuo*. Analysis of the unpurified reaction mixture through the use of <sup>1</sup>H NMR was used to determine the ratio of product to elimination ratio. Silica gel chromatography (pentane) afforded 31.0 mg (90% yield) of a colorless oil of the allyl-allyl coupling product, with less than 5% elimination product.

#### **5. Representative Procedure for PdCl<sub>2</sub>-Catalyzed Coupling (with water, without glovebox technologies).**

A flame-dried 2-dram vial equipped with a magnetic stir bar

was charged with palladium(II) chloride (1.4 mg, 0.008 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and cesium fluoride (91.1 mg, 0.60 mol). The vial was sealed with a septum and purged three times with N<sub>2</sub>. THF (1.0 mL) and deoxygenated water (0.1 mL) were then added by syringe, followed by the addition of *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (49.6 mg, 0.20 mmol) and allylboronic acid pinacol ester (40.4 mg, 0.24 mmol), both by syringe. The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of MgSO<sub>4</sub> (top) and silica gel (bottom) and concentrated *in vacuo*. Analysis of the unpurified reaction mixture through the use of <sup>1</sup>H NMR was used to determine the ratio of product to elimination. Silica gel chromatography (pentane) afforded 30.2 mg (89% yield) of a colorless oil, with 17:1 allyl-allyl coupling product to elimination product.

## 6. Characterization and Proof of Stereochemistry

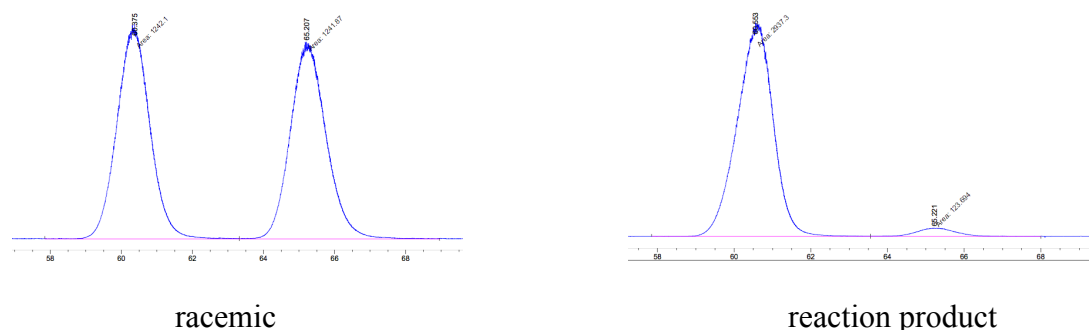

**(*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (4.24).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.38 (3H, s, CH<sub>3</sub>), 2.52 (1H, dd, *J* = 14.0, 7.0 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CH<sub>2</sub>), 2.57 (1H, dd, *J* = 14.0, 7.0 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CH<sub>2</sub>), 4.98-5.14 (4H, m, CCH=CH<sub>2</sub> & CH<sub>2</sub>CH=CH<sub>2</sub>), 5.62 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 6.06 (1H, dd, *J* = 17.0, 11.0 Hz, CCH=CH<sub>2</sub>), 7.18-7.22 (1H, m, Ar-H), 7.30-7.35 (4H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 24.9, 44.0, 45.5, 112.0, 117.2, 125.9, 126.6, 128.1,

135.1, 146.5, 147.0; IR (neat): 3080.8 (w), 3023.5 (w), 3004.7 (w), 2974.9 (w), 2921.5 (w), 1637.6 (w), 1599.9 (w), 1493.1 (w), 1444.5 (w), 1411.6 (w), 1371.5 (w), 1074.6 (w), 1028.9 (w), 995.7 (w), 911.0 (s), 764.2 (s), 697.3 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{17}$  [M+H]: calculated: 173.1330, found: 173.1337;  $[\alpha]_{\text{D}}^{20} = -4.46$  ( $c = 1.54$ ,  $\text{CHCl}_3$ ).<sup>36</sup> The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (31.0 mg, 90% yield), with less than 5% elimination product.  $R_f = 0.75$  (8:1 hexane/EtOAc, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

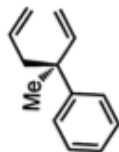
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**. Spectral data and optical rotation are in accordance with literature.<sup>36</sup>

*Chiral GC (CD-GTA, Supelco, 60 °C, 25 psi) - analysis of title compound.*

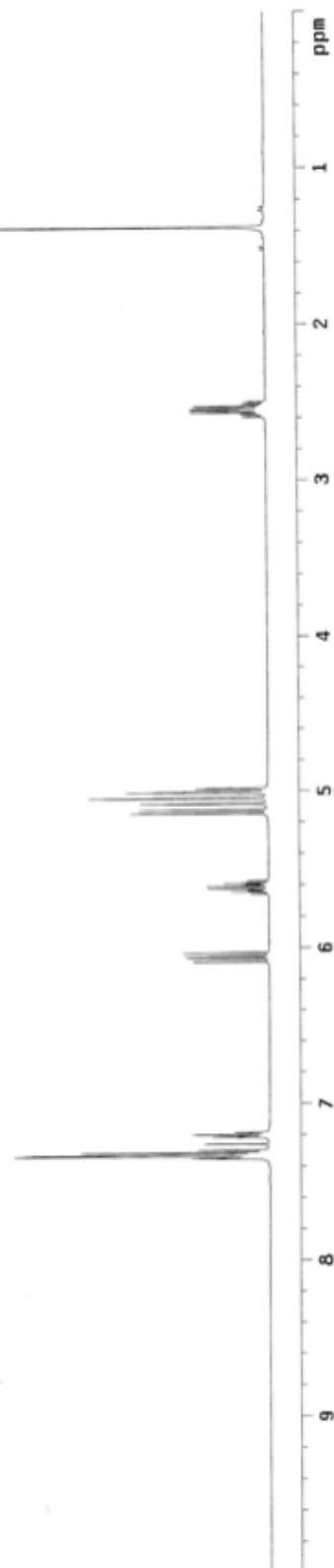


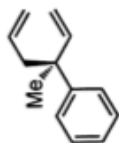
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	60.553	MF	1.0818	2937.30469	45.25162	95.95903
2	65.221	FM	1.1593	123.69395	1.77827	4.04097

<sup>36</sup> Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760.

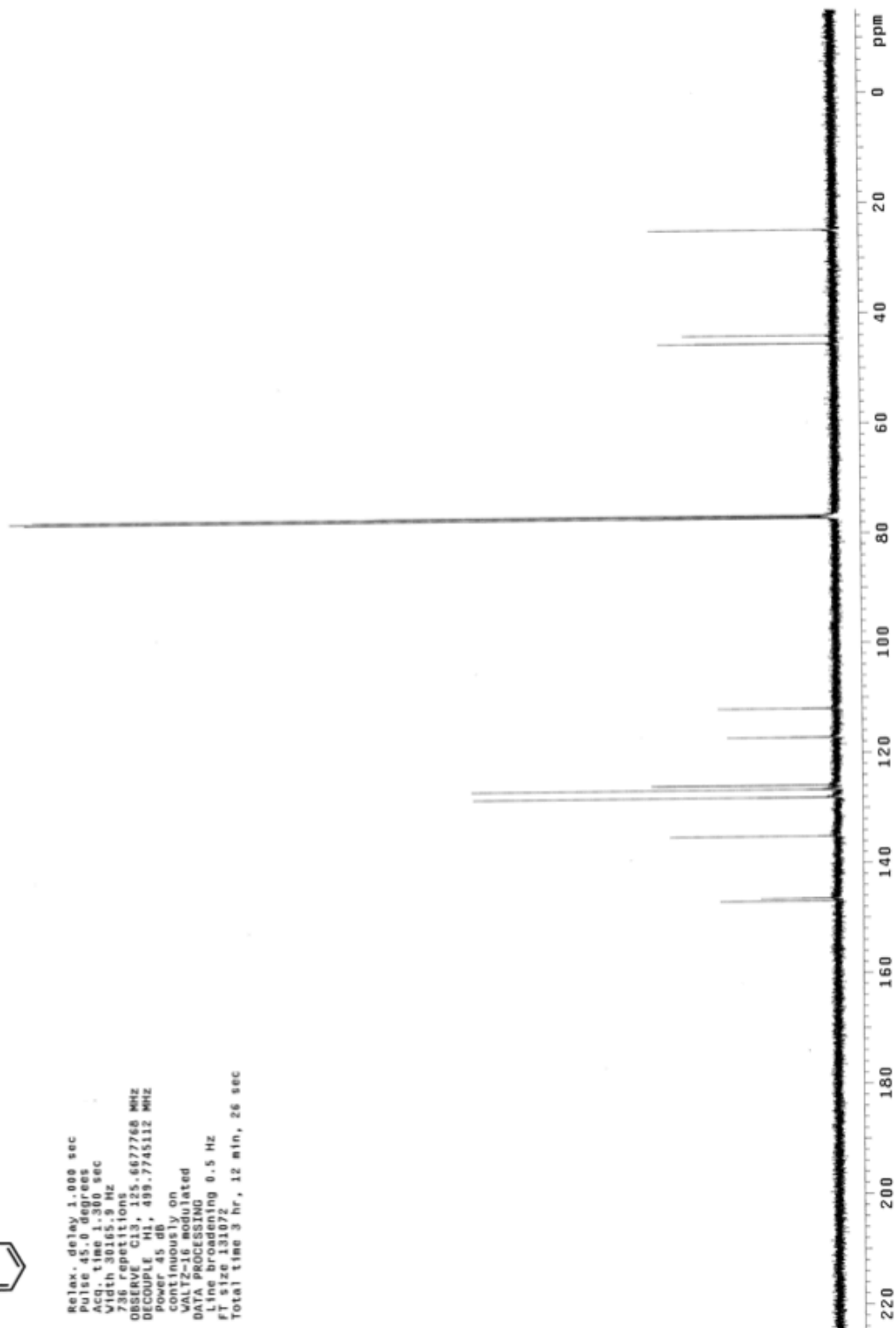


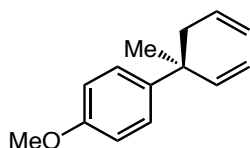
Relax. delay 1.000 sec  
 Pulse 45.0 degrees  
 Acq. time 3.080 sec  
 Width 7096.0 Hz  
 16 repetitions  
 OBSERVE H1, 499.7720254 MHz  
 DATA PROCESSING  
 Resol. enhancement -0.0 Hz  
 FT size 65536  
 Total time 1 min, 12 sec





Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 1.360 sec  
Width 30165.9 Hz  
736 repetitions  
OBSERVE C13, 125.687768 MHz  
DECOUPLE H1, 499.7745112 MHz  
Power 45 dB  
Continuously on  
All 256 scans collected  
MULTISCAN MODE  
DATA PROCESSING  
Line broadening 0.5 Hz  
FT size 131072  
Total time 3 hr, 12 min, 26 sec





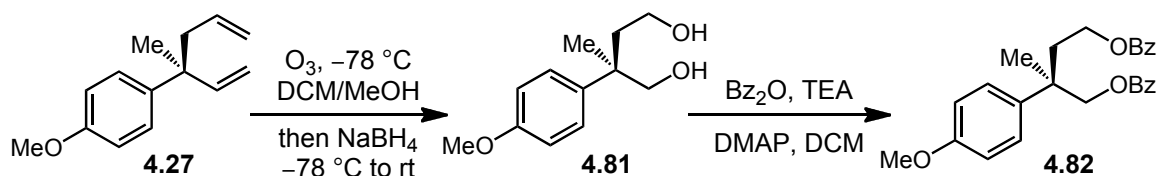
**(S)-1-methoxy-4-(3-methylhexa-1,5-dien-3-yl)benzene (4.27).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.34 (3H, s,  $\text{CH}_3$ ), 2.48 (1H, dd,  $J = 14.0, 7.0$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.53 (1H, dd,  $J = 14.0, 7.0$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 3.79 (3H, s,  $\text{OCH}_3$ ), 4.97-5.10 (4H, m,  $\text{CCH}=\text{CH}_2$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.60 (1H, dddd,  $J = 17.0, 10.0, 7.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.02 (1H, dd,  $J = 17.5, 11.0$  Hz,  $\text{CCH}=\text{CH}_2$ ), 6.83-6.86 (2H, m, Ar-H), 7.22-7.25 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.0, 43.4, 45.6, 55.2, 111.7, 113.4, 117.1, 127.6, 135.2, 139.0, 146.8, 157.6; IR (neat): 3072.7 (w), 3000.7 (w), 2973.7 (w), 2933.0 (w), 2834.5 (w), 1637.1 (w), 1510.3 (s), 1296.3 (m), 1246.3 (s), 1181.1 (s), 1035.5 (s), 996.3 (m), 910.4 (s), 826.6 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{19}\text{O}$   $[\text{M}+\text{H}]$ : calculated: 203.1436, found: 203.1443;  $[\alpha]_D^{20} = -6.03$  ( $c = 1.14$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (50:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (42.0 mg, 83% yield), with 12:1 allyl-allyl coupling product to elimination product.  $R_f = 0.56$  (8:1 hexanes/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ ).

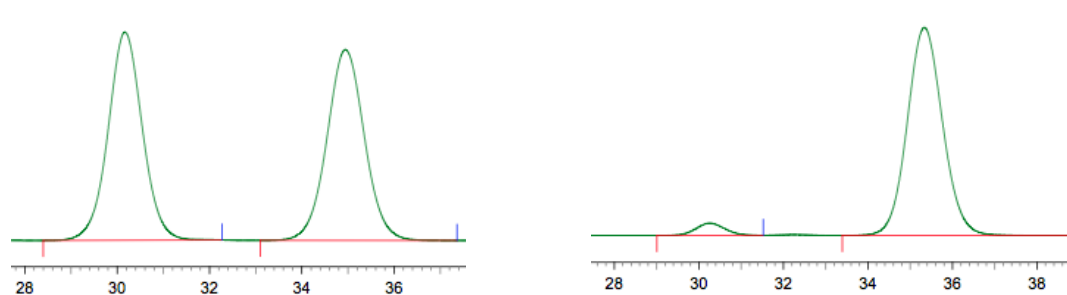


### Proof of Stereochemistry:

The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester (**4.83**) for HPLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by X-ray crystallographic analysis (anomalous dispersion) of the diol (**4.81**).



Chiral HPLC (AD-H, Chirapak, 1 mL/min, 2% isopropanol, 220 nm) – analysis of 2-(4-methoxyphenyl)-2-methylbutane-1,4-diyl dibenzoate (**4.83**).



racemic

reaction product

Retention Time	Area	Area %	Height	Height %
30.257	55422548	4.61	1151133	5.53
35.337	1146702137	95.39	19674468	94.47
Totals	1202124685	100.00	20825601	100.00

## X-Ray Crystallographic Data for 4.81

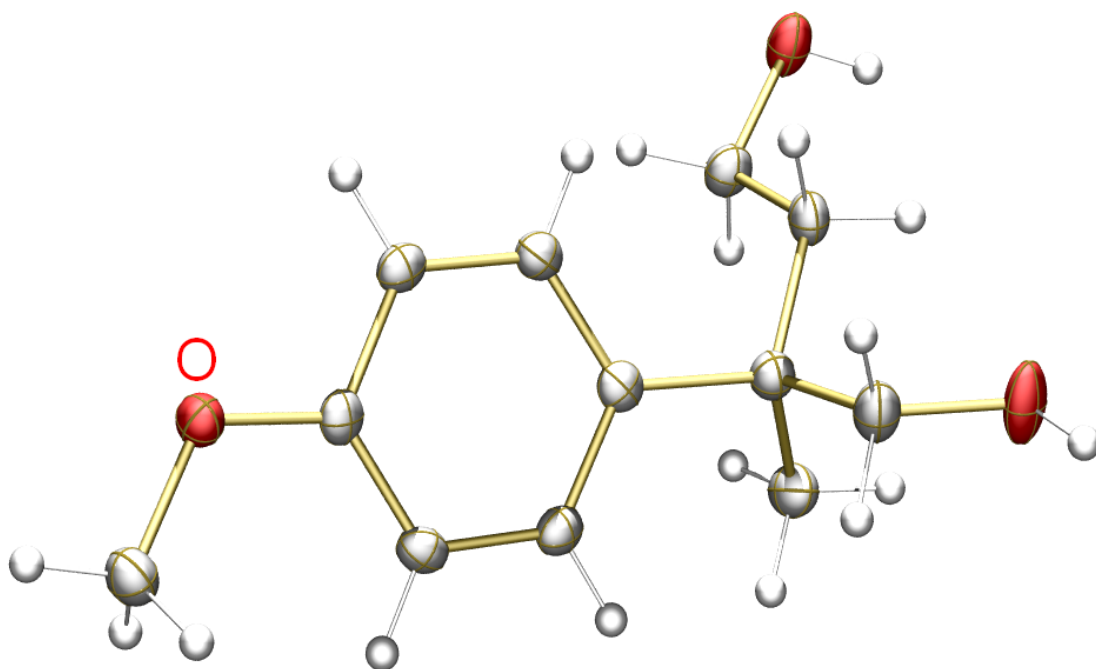
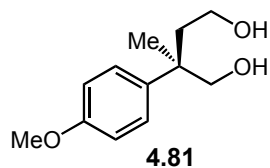


Table 1. Crystal data and structure refinement for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>.

Identification code	C <sub>12</sub> H <sub>18</sub> O <sub>3</sub>	
Empirical formula	C <sub>12</sub> H <sub>18</sub> O <sub>3</sub>	
Formula weight	210.26	
Temperature	100(2) K	
Wavelength	1.54178 $\approx$	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	$a = 5.8880(2) \approx$	$\alpha = 90^\circ.$
	$b = 7.5873(3) \approx$	$\beta = 101.821(2)^\circ.$
	$c = 12.5089(5) \approx$	$\gamma = 90^\circ.$
Volume	$546.97(4) \approx^3$	

Z	2
Density (calculated)	1.277 Mg/m <sup>3</sup>
Absorption coefficient	0.732 mm <sup>-1</sup>
F(000)	228
Crystal size	0.10 x 0.06 x 0.02 mm <sup>3</sup>
Theta range for data collection	3.61 to 68.16°.
Index ranges	-7<=h<=6, -9<=k<=8, -15<=l<=15
Reflections collected	7510
Independent reflections	1859 [R(int) = 0.0281]
Completeness to theta = 68.16°	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9855 and 0.9304
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	1859 / 3 / 142
Goodness-of-fit on F <sup>2</sup>	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0828
R indices (all data)	R1 = 0.0325, wR2 = 0.0838
Absolute structure parameter	0.05(19)
Extinction coefficient	na
Largest diff. peak and hole	0.216 and -0.158 e. <sup>-3</sup>

Table 2. Atomic coordinates (  $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\approx 2 \times 10^3$ ) for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>. U(eq) is defined as one third of the trace of the orthogonalized U<sub>ij</sub> tensor.

	x	y	z	U(eq)
O(1)	5875(2)	4852(1)	-1273(1)	22(1)
O(2)	14611(2)	1066(2)	3945(1)	28(1)
O(3)	13718(3)	7591(2)	4063(1)	35(1)
C(1)	7003(3)	4947(2)	-206(1)	18(1)
C(2)	9102(3)	4038(2)	63(1)	19(1)
C(3)	10404(3)	4103(2)	1116(1)	19(1)

C(4)	9658(3)	5045(2)	1945(1)	19(1)
C(5)	7537(3)	5908(2)	1655(1)	20(1)
C(6)	6206(3)	5870(2)	601(1)	19(1)
C(7)	3712(3)	5764(2)	-1573(1)	25(1)
C(8)	11174(3)	5300(2)	3089(1)	21(1)
C(9)	9724(3)	5231(3)	3982(1)	27(1)
C(10)	13205(3)	3989(2)	3359(1)	21(1)
C(11)	12571(3)	2069(2)	3496(1)	23(1)
C(12)	12204(3)	7156(2)	3056(1)	25(1)

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Table 3. Bond lengths [ $\approx$ ] and angles [ $\infty$ ] for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>.

O(1)-C(1)	1.3659(18)
O(1)-C(7)	1.430(2)
O(2)-C(11)	1.436(2)
O(2)-H(2O)	0.851(16)
O(3)-C(12)	1.425(2)
O(3)-H(3O)	0.839(17)
C(1)-C(6)	1.387(2)
C(1)-C(2)	1.395(2)
C(2)-C(3)	1.383(2)
C(2)-H(2B)	0.9500
C(3)-C(4)	1.401(2)
C(3)-H(3B)	0.9500
C(4)-C(5)	1.391(2)
C(4)-C(8)	1.536(2)
C(5)-C(6)	1.389(2)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800

C(8)-C(12)	1.538(2)
C(8)-C(10)	1.539(2)
C(8)-C(9)	1.540(2)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.522(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(1)-O(1)-C(7)	117.36(12)
C(11)-O(2)-H(2O)	107.1(16)
C(12)-O(3)-H(3O)	110.6(17)
O(1)-C(1)-C(6)	124.63(14)
O(1)-C(1)-C(2)	116.05(13)
C(6)-C(1)-C(2)	119.32(14)
C(3)-C(2)-C(1)	120.19(14)
C(3)-C(2)-H(2B)	119.9
C(1)-C(2)-H(2B)	119.9
C(2)-C(3)-C(4)	121.77(14)
C(2)-C(3)-H(3B)	119.1
C(4)-C(3)-H(3B)	119.1
C(5)-C(4)-C(3)	116.60(14)
C(5)-C(4)-C(8)	120.21(14)
C(3)-C(4)-C(8)	122.88(14)
C(6)-C(5)-C(4)	122.65(14)
C(6)-C(5)-H(5A)	118.7
C(4)-C(5)-H(5A)	118.7
C(1)-C(6)-C(5)	119.45(14)
C(1)-C(6)-H(6A)	120.3

C(5)-C(6)-H(6A)	120.3
O(1)-C(7)-H(7A)	109.5
O(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
O(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(4)-C(8)-C(12)	104.31(13)
C(4)-C(8)-C(10)	113.60(13)
C(12)-C(8)-C(10)	107.78(13)
C(4)-C(8)-C(9)	111.65(13)
C(12)-C(8)-C(9)	109.33(14)
C(10)-C(8)-C(9)	109.90(13)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(11)-C(10)-C(8)	116.45(14)
C(11)-C(10)-H(10A)	108.2
C(8)-C(10)-H(10A)	108.2
C(11)-C(10)-H(10B)	108.2
C(8)-C(10)-H(10B)	108.2
H(10A)-C(10)-H(10B)	107.3
O(2)-C(11)-C(10)	110.24(14)
O(2)-C(11)-H(11A)	109.6
C(10)-C(11)-H(11A)	109.6
O(2)-C(11)-H(11B)	109.6
C(10)-C(11)-H(11B)	109.6
H(11A)-C(11)-H(11B)	108.1
O(3)-C(12)-C(8)	111.52(13)
O(3)-C(12)-H(12A)	109.3
C(8)-C(12)-H(12A)	109.3

O(3)-C(12)-H(12B)	109.3
C(8)-C(12)-H(12B)	109.3
H(12A)-C(12)-H(12B)	108.0

---

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ( $\approx \times 10^3$ ) for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>. The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U <sup>11</sup>	U <sup>22</sup>	U <sup>33</sup>	U <sup>23</sup>	U <sup>13</sup>	U <sup>12</sup>
O(1)	23(1)	21(1)	20(1)	0(1)	1(1)	2(1)
O(2)	40(1)	17(1)	24(1)	-1(1)	-6(1)	4(1)
O(3)	49(1)	13(1)	32(1)	1(1)	-15(1)	-4(1)
C(1)	22(1)	12(1)	20(1)	1(1)	2(1)	-3(1)
C(2)	22(1)	14(1)	22(1)	-1(1)	6(1)	-1(1)
C(3)	19(1)	15(1)	24(1)	1(1)	4(1)	0(1)
C(4)	20(1)	14(1)	22(1)	2(1)	4(1)	-2(1)
C(5)	22(1)	16(1)	23(1)	-2(1)	6(1)	-2(1)
C(6)	19(1)	14(1)	25(1)	3(1)	4(1)	2(1)
C(7)	23(1)	24(1)	26(1)	2(1)	1(1)	2(1)
C(8)	21(1)	18(1)	21(1)	-1(1)	2(1)	1(1)
C(9)	27(1)	31(1)	21(1)	-1(1)	3(1)	3(1)
C(10)	22(1)	20(1)	19(1)	0(1)	-1(1)	-1(1)
C(11)	29(1)	16(1)	24(1)	0(1)	3(1)	2(1)
C(12)	28(1)	17(1)	25(1)	1(1)	-4(1)	0(1)

---

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\approx^2 \times 10^{-3}$ ) for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>.

	x	y	z	U(eq)
H(2O)	15150(40)	1480(30)	4579(14)	43
H(3O)	14020(40)	8670(20)	4090(20)	52
H(2B)	9638	3373	-479	23
H(3B)	11842	3494	1282	23
H(5A)	6976	6549	2200	24
H(6A)	4762	6472	434	23
H(7A)	3081	5595	-2354	37
H(7B)	3956	7025	-1420	37
H(7C)	2616	5298	-1150	37
H(9A)	8439	6072	3808	40
H(9B)	10707	5536	4689	40
H(9C)	9103	4039	4019	40
H(10A)	14099	4054	2770	25
H(10B)	14246	4379	4043	25
H(11A)	11452	1993	3986	28
H(11B)	11822	1574	2777	28
H(12A)	13071	7218	2458	30
H(12B)	10928	8029	2901	30

Table 6. Torsion angles [ $^\circ$ ] for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>.

C(7)-O(1)-C(1)-C(6)	-0.4(2)
C(7)-O(1)-C(1)-C(2)	179.72(14)
O(1)-C(1)-C(2)-C(3)	177.96(13)
C(6)-C(1)-C(2)-C(3)	-1.9(2)
C(1)-C(2)-C(3)-C(4)	1.1(2)



C(2)-C(3)-C(4)-C(5)	0.1(2)
C(2)-C(3)-C(4)-C(8)	-173.51(15)
C(3)-C(4)-C(5)-C(6)	-0.6(2)
C(8)-C(4)-C(5)-C(6)	173.28(15)
O(1)-C(1)-C(6)-C(5)	-178.35(15)
C(2)-C(1)-C(6)-C(5)	1.5(2)
C(4)-C(5)-C(6)-C(1)	-0.3(2)
C(5)-C(4)-C(8)-C(12)	-74.41(18)
C(3)-C(4)-C(8)-C(12)	99.03(17)
C(5)-C(4)-C(8)-C(10)	168.51(14)
C(3)-C(4)-C(8)-C(10)	-18.1(2)
C(5)-C(4)-C(8)-C(9)	43.6(2)
C(3)-C(4)-C(8)-C(9)	-143.01(16)
C(4)-C(8)-C(10)-C(11)	-68.29(18)
C(12)-C(8)-C(10)-C(11)	176.66(14)
C(9)-C(8)-C(10)-C(11)	57.60(19)
C(8)-C(10)-C(11)-O(2)	-168.99(12)
C(4)-C(8)-C(12)-O(3)	-178.69(14)
C(10)-C(8)-C(12)-O(3)	-57.66(17)
C(9)-C(8)-C(12)-O(3)	61.77(18)

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Symmetry transformations used to generate equivalent atoms:

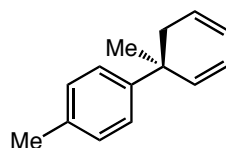
Table 7. Hydrogen bonds for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> [ $\approx$  and  $\infty$ ].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(3)#1	0.851(16)	1.891(17)	2.7404(17)	175(2)
O(3)-H(3O)...O(2)#2	0.839(17)	1.865(18)	2.6989(18)	172(2)

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Symmetry transformations used to generate equivalent atoms:

#1 -x+3,y-1/2,-z+1   #2 x,y+1,z



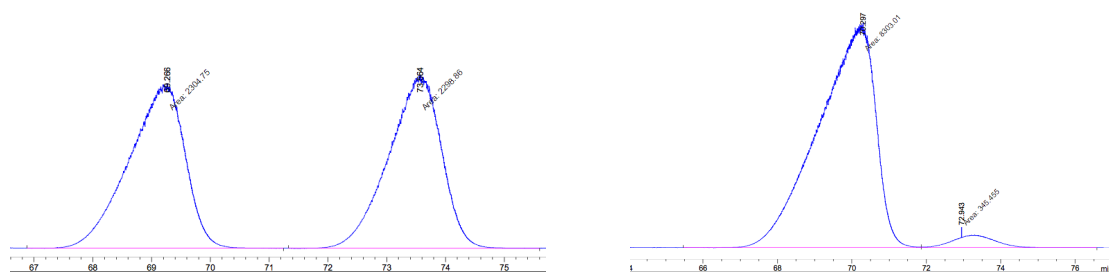
**(S)-1-methyl-4-(3-methylhexa-1,5-dien-3-yl)benzene (4.32).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (3H, s,  $\text{CH}_3\text{CCH}=\text{CH}_2$ ), 2.33 (3H, s,  $\text{ArCH}_3$ ), 2.50 (1H, dddd,  $J = 14.0, 7.0, 1.5, 1.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.55 (1H, dddd,  $J = 14.0, 7.0, 1.5, 1.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 4.97-5.06 (3H, m,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.11 (1H, dd,  $J = 10.5, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.61 (1H, dddd,  $J = 17.0, 10.0, 7.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.03 (1H, dd,  $J = 17.0, 10.5$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.11-7.13 (2H, m, Ar-H), 7.21-7.23 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.9, 24.9, 43.7, 45.5, 111.8, 117.1, 126.5, 128.8, 135.2, 135.3, 144.0, 146.7; IR (neat): 3078.6 (w), 3003.5 (w), 2974.6 (w), 2921.4 (w), 1638.1 (s), 1512.9 (m), 1454.7 (w), 1412.8 (w), 1370.5 (w), 996.0 (m), 910.9 (s), 814.1 (s), 728.6 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{19}$   $[\text{M}+\text{H}]$ : calculated: 187.1487, found: 187.1477;  $[\alpha]_{\text{D}}^{20} = -2.88$  ( $c = 1.83$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (27.9 mg, 76% yield), with 17:1 allyl-allyl coupling product to elimination product.  $R_f = 0.63$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

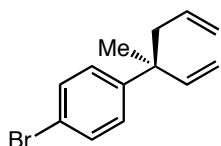
*Chiral GC (CD-GTA, Supelco, 70 °C, 25 psi) - analysis of title compound.*



racemic

reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	70.297	MF	1.7618	8303.00879	78.54633	96.00559
2	72.943	FM	0.7885	345.45468	7.30192	3.99441



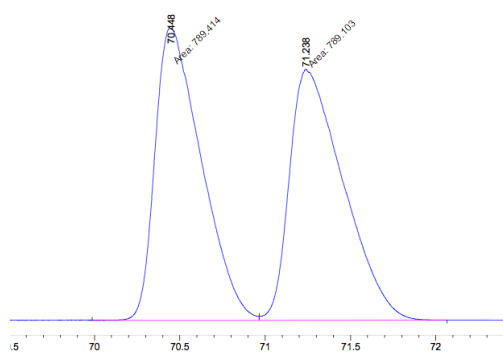
**(S)-1-bromo-4-(3-methylhexa-1,5-dien-3-yl)benzene (4.43).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.34 (3H, s,  $\text{CH}_3$ ), 2.48 (1H, dd,  $J = 13.5$ , 7.5 Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.52 (1H, dd,  $J = 13.5$ , 7.5 Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 4.99-5.06 (3H, m,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.14 (1H, dd,  $J = 10.5$ , 1.0 Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.57 (1H, dddd,  $J = 17.0$ , 10.0, 7.5, 7.5 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.00 (1H, dd,  $J = 17.5$ , 10.5 Hz,  $\text{CCH}=\text{CH}_2$ ), 7.18-7.21 (2H, m, Ar-H), 7.40-7.43 (2H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.9, 43.9, 45.4, 112.5, 117.6, 119.8, 128.6, 131.1, 134.6, 145.9, 146.0; IR (neat): 3097.2 (w), 3004.2 (w), 2974.9 (w), 2919.3 (w), 2849.9 (w), 1637.9 (w), 1489.7 (m), 1412.9 (w), 1106.4 (m), 1007.5 (s), 912.5 (s), 818.9 (s), 729.3 (m), 533.8 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{16}\text{Br}$  [ $\text{M}+\text{H}$ ]: calculated: 251.0435, found: 251.0430;  $[\alpha]_D^{20} = -5.36$  ( $c = 2.51$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (44.7 mg, 90% yield), with 20:1 allyl-allyl coupling product to elimination product.  $R_f = 0.72$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

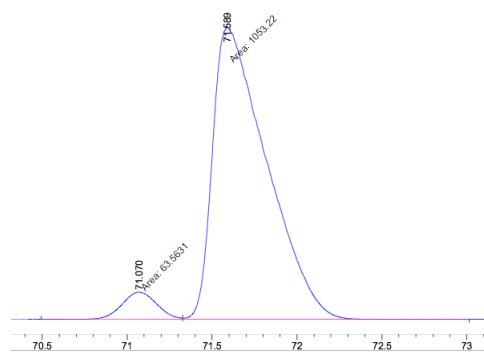
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

*Chiral GC ( $\beta$ -dex, Supelco, 100 °C 10 min, ramp 0.5 deg/min to 180 °C, 25 psi) - analysis of title compound.*

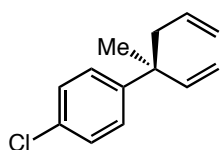


racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	71.070	MF	0.2384	63.56308	4.44339	5.69163
2	71.589	FM	0.3674	1053.21863	47.77425	94.30837



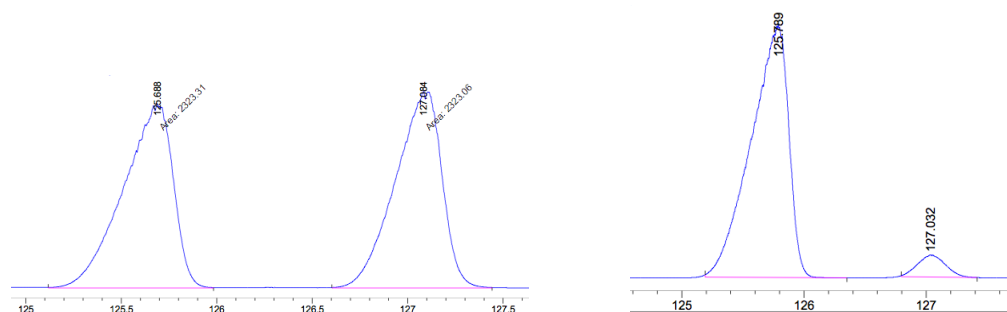
**(S)-1-chloro-4-(3-methylhexa-1,5-dien-3-yl)benzene (4.44).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (3H, s,  $\text{CCH}_3$ ), 2.48 (1H, dd,  $J = 13.9, 7.2$  Hz,  $\text{CH}_a\text{H}_b\text{C}=\text{CH}_2$ ), 2.53 (1H, dd,  $J = 13.9, 7.2$  Hz,  $\text{CH}_a\text{H}_b\text{C}=\text{CH}_2$ ), 4.99-5.06 (3H, m,  $\text{CCH}=\text{CH}_{cis}\text{H}_{trans}$  &  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.13 (1H, d,  $J = 10.8$  Hz,  $\text{CCH}=\text{CH}_{cis}$ ), 5.57 (1H, dddd,  $J = 16.8, 9.8, 7.2, 7.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.00 (1H, dd,  $J = 17.6, 10.8$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.24-7.28 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.9, 43.8, 45.5, 112.4, 117.6, 128.1, 128.2, 131.7, 134.6, 145.5, 146.0; IR (neat): 3081.2 (w), 2924.1 (s), 2867.5 (m), 1638.9 (w), 1493.3 (s), 1461.0 (w), 1399.5 (w), 1372.0 (w), 1097.1 (m), 1012.8 (s), 995.8 (m), 915.6 (s), 825.2 (s), 748.7 (w), 536.6 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{16}\text{Cl}$  [M+H]: calculated: 207.0941, found: 207.0940;  $[\alpha]_D^{20} = -2.1$  ( $c = 0.40$ ,  $\text{CHCl}_3$ ). The unpurified material was purified on silica gel (pentane) to afford a clear, colorless oil (50.8 mg, 70% yield), with less than 5% elimination product.  $R_f = 0.70$  (pentane, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

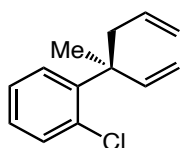
*Chiral GC (CD-GTA, Supelco, 60 °C, 80 min, 1.0 deg/min to 120 °C, 25 psi)-analysis of title compound.*



racemic

reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	125.789	BB	0.2567	3800.16162	177.55411	93.86945
2	127.032	BB	0.1903	248.18599	15.54616	6.13055



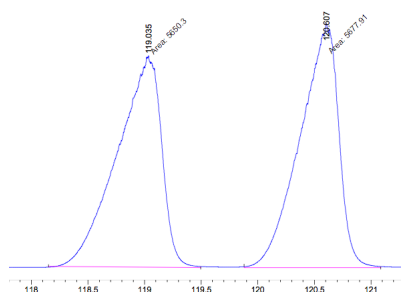
**(S)-1-chloro-2-(3-methylhexa-1,5-dien-3-yl)benzene (4.45).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.49 (3H, s,  $\text{CCH}_3$ ), 2.63 (1H, dd,  $J = 13.9, 7.2$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 3.02 (1H, dd,  $J = 13.9, 7.2$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 4.93-4.96 (m, 2H,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$  &  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.03 (1H, m,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.10 (1H, dd,  $J = 10.7, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.52 (1H, dddd,  $J = 17.0, 10.3, 7.2, 7.2$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.20 (1H, dd,  $J = 17.6, 10.7$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.14-7.17 (1H, m, Ar-H), 7.19-7.22 (1H, m, Ar-H), 7.33-7.35 (1H, m, Ar-H), 7.36-7.38 (1H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.7, 42.9, 45.0, 112.3, 117.3, 126.4, 127.6, 129.2, 131.7, 133.8, 134.8, 143.2, 145.7; IR (neat): 3077.2 (w), 3003.9 (w), 2975.9 (w), 2921.8 (w), 1638.5 (w), 1468.2 (m), 1430.2 (m), 1411.7 (m), 1037.9 (m), 993.6 (m), 913.6 (s), 860.0 (m), 757.0 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{16}\text{Cl}$   $[\text{M}+\text{H}]^+$ : calculated: 207.0941, found: 207.0940.  $[\alpha]_D^{20} = -26.0$  ( $c = 0.97$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (38.3 mg, 97% yield), with 4:1 allyl-allyl coupling product to elimination product.  $R_f = 0.58$  (pentane, stain in  $\text{KMnO}_4$ ).



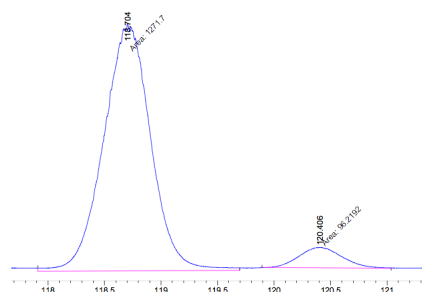
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

*Chiral GC (CD-GTA, Supelco, 60 °C, 80 min, 1.0 deg/min to 120 °C, 25 psi)-analysis of the title compound.*

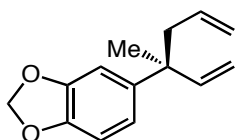


racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	118.704	MM	0.4831	1271.70264	43.87696	92.96603
2	120.406	MM	0.4385	96.21922	3.65722	7.03397



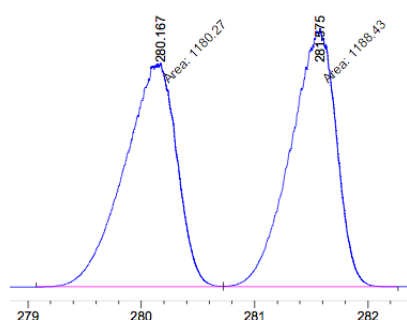
**(S)-5-(3-methylhexa-1,5-dien-3-yl)benzo[d][1,3]dioxole (4.47).**  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.32 (3H, s,  $\text{CCH}_3$ ), 2.46 (1H, dd,  $J = 13.8, 7.1$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.51 (1H, dd,  $J = 13.8, 7.1$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 4.98-5.03 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.04 (1H, dd,  $J = 17.4, 1.1$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.10 (1H, dd,  $J = 10.8, 1.1$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.60 (1H, dddd, 17.4, 10.3, 7.1, 7.1 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.93 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.00 (1H, dd,  $J = 17.4, 10.8$  Hz,  $\text{CCH}=\text{CH}_2$ ), 6.73-6.78 (2H, m, Ar-H), 6.82-6.84 (1H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.2, 43.9, 45.6, 100.8, 107.6, 107.7, 111.9, 117.3, 119.5, 135.0, 141.1, 145.5, 146.6, 147.5; IR (neat): 3077.7 (w), 2971.8 (w), 2922.9 (w), 2775.6 (w), 1637.9 (w), 1503.8 (m), 1485.1 (s), 1431.9 (m), 1232.4 (s), 1039.7 (s), 938.4 (m), 912.5 (s), 808.5 (m), 554.3 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{17}\text{O}_2$   $[\text{M}+\text{H}]^+$ : calculated: 217.1229, found: 217.1224;  $[\alpha]_D^{20} = -1.6$  ( $c = 0.69$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (39.4 mg, 94% yield), with 6:1 allyl-allyl coupling product to elimination product.  $R_f = 0.39$  (pentane, stain in  $\text{KMnO}_4$ ).

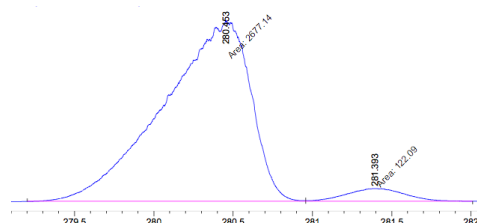
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

*Chiral GLC (CD-GTA, Supelco, 55 °C, 25 psi) analysis of title compound.*

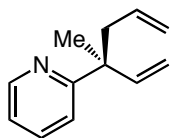


racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	280.453	MM	0.6316	2677.13745	70.64734	95.63845
2	281.393	MM	0.4152	122.08971	4.90134	4.36155

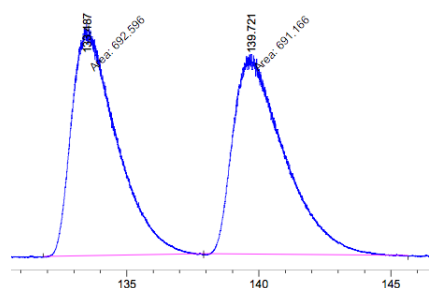


**(S)-2-(3-methylhexa-1,5-dien-3-yl)pyridine (4.48).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.42 (3H, s,  $\text{CCH}_3$ ), 2.61 (1H, dddd,  $J = 13.9, 7.0, 1.3, 1.3$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 2.70 (1H, dddd,  $J = 13.9, 7.5, 1.3, 1.3$  Hz,  $\text{CH}_a\text{H}_b\text{CH}=\text{CH}_2$ ), 4.97 (1H, dddd,  $J = 9.6, 2.2, 1.3, 1.3$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.01 (1H, dddd,  $J = 17.0, 2.2, 1.3, 1.3$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.09 (1H, dd,  $J = 17.5, 1.2$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.16 (1H, dd,  $J = 10.8, 1.2$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.62 (1H, dddd,  $J = 17.0, 9.6, 7.5, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.19 (1H, dd,  $J = 17.5, 10.8$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.10 (1H, ddd,  $J = 5.9, 4.9, 1.2$  Hz, Ar-H), 7.28 (1H, ddd,  $J = 8.1, 1.0, 1.0$  Hz, Ar-H), 7.60 (1H, ddd,  $J = 8.0, 7.3, 1.9$  Hz, Ar-H), 8.59 (1H, dq,  $J = 4.7, 1.0$  Hz, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.5, 45.0, 46.7, 112.6, 117.3, 121.0, 121.1, 135.1, 136.1, 145.5, 148.8, 165.9; IR (neat): 3079.3 (w), 3004.4 (m), 2975.2 (m), 2926.7 (w), 1638.1 (m), 1587.5 (s), 1569.7 (m), 1468.5 (m), 1430.0 (m), 1047.1 (m), 913.4 (s), 788.4 (m), 747.1 (s), 402.7 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{16}\text{N}$   $[\text{M}+\text{H}]^+$ : calculated: 174.1283, found: 174.1291;  $[\alpha]_{\text{D}}^{20} = +28.4$  ( $c = 0.36$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (19:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (40.0 mg, 81% yield), with less than 5% elimination product.  $R_f = 0.26$  (9:1 pentane/ $\text{Et}_2\text{O}$ , stain in  $\text{KMnO}_4$ ).

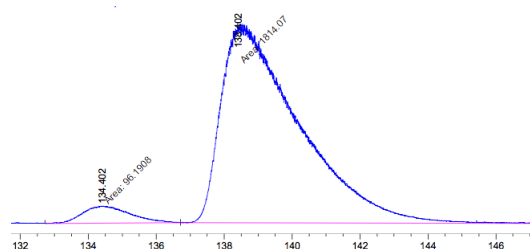
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

*Chiral GC (CD-GTA, Supelco, 55 °C, 25 psi )-analysis of title compound.*

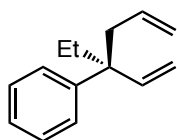


racemic



reaction product

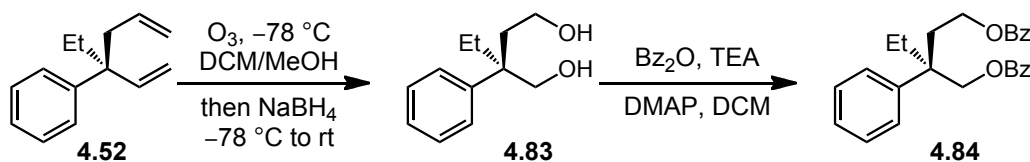
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	134.402	MM	1.6146	96.19075	9.92949e-1	5.03547
2	138.402	MM	2.6311	1814.07385	11.49119	94.96453



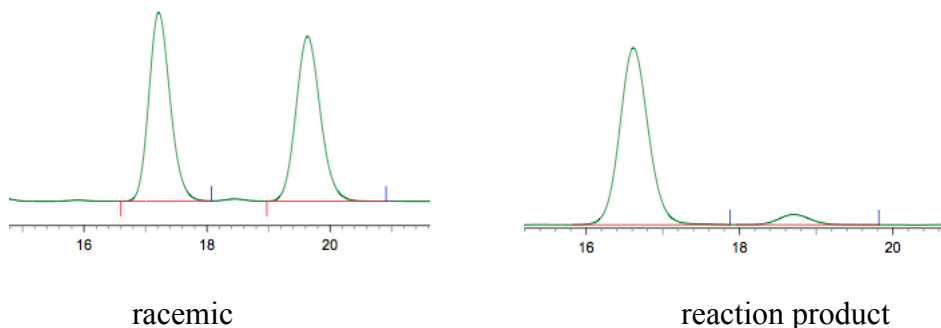
**(S)-(3-ethylhexa-1,5-dien-3-yl)benzene (4.52).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.75 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 1.78 (1H, dq,  $J = 13.5, 7.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}_3$ ), 1.84 (1H, dq,  $J = 13.5, 7.5$  Hz,  $\text{CH}_a\text{H}_b\text{CH}_3$ ), 2.55 (2H, d,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.98 (1H, dddd,  $J = 10.5, 2.5, 1.5, 1.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.02 (1H, dddd,  $J = 17.0, 2.0, 1.5, 1.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.10 (1H, dd,  $J = 17.5, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.22 (1H, dd,  $J = 11.0, 1.5$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.59 (1H, ddt,  $J = 17.5, 10.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.94 (1H, dd,  $J = 17.5, 11.0$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.18-7.21 (1H, m, Ar-H), 7.29-7.33 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.3, 29.4, 41.2, 47.6, 113.0, 116.9, 125.8, 127.4, 127.9, 135.0, 145.2, 145.5; IR (neat): 3081.4 (w), 3023.4 (w), 3003.9 (w), 2969.5 (w), 2928.9 (w), 2878.8 (w), 1637.3 (w), 1599.2 (w), 1493.5 (w), 1445.0 (m), 1032.3 (m), 910.7 (s), 782.1 (m), 720.2 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{14}\text{H}_{19}$   $[\text{M}+\text{H}]$ : calculated: 187.1487, found: 187.1486;  $[\alpha]_{\text{D}}^{20} = -18.3$  ( $c = 0.87$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (34.9 mg, 97% yield), with 6:1 allyl-allyl coupling product to elimination product.  $R_f = 0.80$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

### Proof of Stereochemistry:

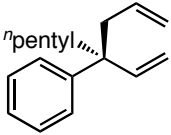
The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester (**4.84**) for HPLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.



*Chiral HPLC (AD-H, Chiralpak, 1 mL/min, 2% isopropanol, 220 nm) – analysis of 2-ethyl-2-phenylbutane-1,4-diyl dibenzoate (**4.84**).*

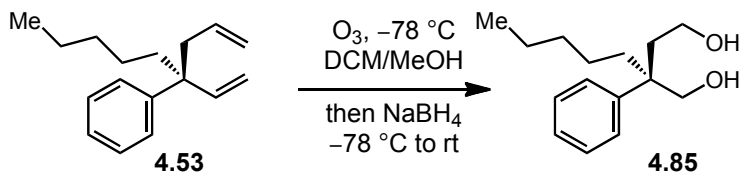


Retention Time	Area	Area %	Height	Height %
16.617	52915233	93.90	2028796	94.50
18.707	3435601	6.10	118052	5.50
Totals	56350834	100.00	2146848	100.00


**(S)-(4-vinylnon-1-en-4-yl)benzene (4.53).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.83 (3H, t,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 1.05-1.29 (6H, m,  $(\text{CH}_2)_3\text{CH}_3$ ), 1.67-1.79 (2H, m,  $\text{CH}_2(\text{CH}_2)_3\text{CH}_3$ ), 2.55 (2H, d,  $J = 7.5$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.96-5.02 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.08 (1H, dd,  $J = 17.0, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.19 (1H, dd,  $J = 10.5, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.58 (1H, ddt,  $J = 17.0, 10.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.94 (1H, dd,  $J = 17.0, 10.5$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.16-7.20 (1H, m, Ar-H), 7.28-7.32 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.1, 22.5, 23.4, 32.5, 37.1, 41.9, 47.3, 112.7, 116.9, 125.8, 127.3, 127.9, 135.1, 145.5, 145.8; IR (neat): 3081.1 (w), 3004.0 (w), 2930.7 (m), 2860.5 (w), 1637.5 (w), 1493.8 (w), 1445.3 (m), 1378.1 (w), 1073.2 (m), 910.6 (s), 697.8 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{17}\text{H}_{25}$   $[\text{M}+\text{H}]$ : calculated: 229.1956, found: 229.1954;  $[\alpha]_D^{20} = -5.29$  ( $c = 1.69$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (34.6 mg, 78% yield), with 6:1 allyl-allyl coupling product to elimination product.  $R_f = 0.86$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

The title compound was subjected to ozonolysis and reduction, as depicted below. The resulting diol (**4.85**) was analyzed by chiral SFC. The analogous racemic material was prepared *via* the same route through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.

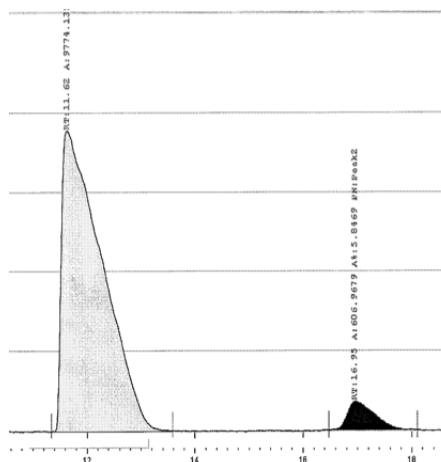




*Chiral SFC (AS-H, Chiralpak, 3 mL/min, 3% methanol, 220 nm) – analysis of 2-pentyl-2-phenylbutane-1,4-diol (4.85).*

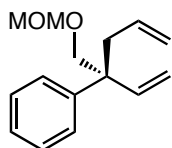


racemic



reaction product

Peak Name	Number	Concentration	Area %	Area	Area Sum
Peak1	1	0	94.1531	9774.1352	
Peak2	2	0	5.8469	606.9679	10381.1031
RT (min)	St. (min)	End (min)	Height		
11.62	11.3404	13.5842	189.5781		
16.95	16.4748	18.0968	17.9589		

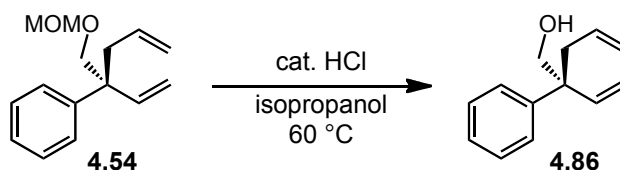


**(R)-3-((methoxymethoxy)methyl)hexa-1,5-dien-3-ylbenzene (4.54).**

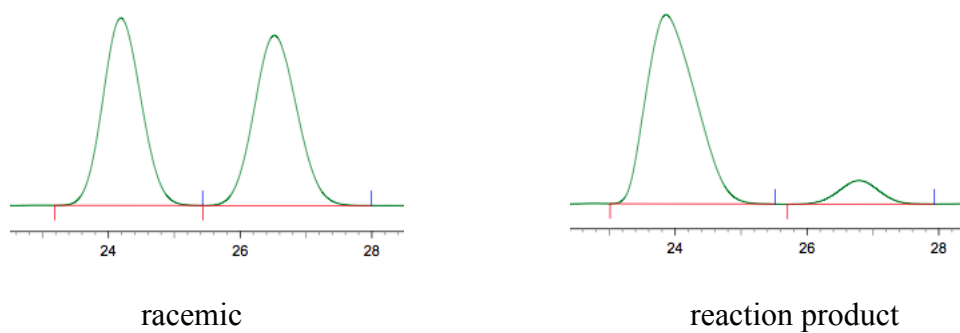
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.67 (2H, d,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.25 (3H, s,  $\text{OCH}_3$ ), 3.78 (1H, d,  $J = 9.0$  Hz,  $\text{CCH}_a\text{H}_b\text{O}$ ), 3.84 (1H, d,  $J = 9.0$  Hz,  $\text{CCH}_a\text{H}_b\text{O}$ ), 4.56 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_a\text{H}_b\text{O}$ ), 4.59 (1H, d,  $J = 6.5$  Hz,  $\text{OCH}_a\text{H}_b\text{O}$ ), 5.01 (1H, dddd,  $J = 10.0, 2.0, 1.5, 1.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.06 (1H, dddd,  $J = 17.0, 2.0, 1.5, 1.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.12 (1H, dd,  $J = 17.0, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.26 (1H, dd,  $J = 11.0, 1.0$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.64 (1H, ddt,  $J = 17.0, 10.0, 7.0$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.04 (1H, dd,  $J = 17.0, 11.0$  Hz,  $\text{CCH}=\text{CH}_2$ ), 7.19-7.23 (1H, m, Ar-H), 7.30-7.36 (4H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  40.3, 48.2, 55.3, 72.5, 96.7, 114.2, 117.7, 126.3, 127.4, 128.0, 134.4, 142.8, 143.4; IR (neat): 3170.5 (w), 3081.9 (w), 2978.5 (m), 2925.9 (w), 2822.2 (w), 1638.2 (w), 1600.1 (w), 1495.3 (w), 1466.8 (w), 1290.2 (w), 1215.8 (m), 1150.9 (m), 1110.5 (s), 998.5 (s), 748.5 (m)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{21}\text{O}_2$   $[\text{M}+\text{H}]^+$ : calculated: 233.1542, found: 233.1551;  $[\alpha]_D^{20} = +0.850$  ( $c = 1.94$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (100:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (26.9 mg, 58% yield), with less than 5% elimination product.  $R_f = 0.51$  (8:1 hexanes/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ ).

### *Proof of Stereochemistry:*

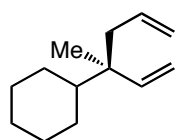
The title compound was subjected to acid-catalyzed MOM deprotection, as depicted below. The resulting alcohol (**4.86**) was subjected to HPLC analysis. The analogous racemic material was prepared *via* the same route through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to **4.27**.



*Chiral HPLC (OD-R, Chiracel, 0.5 mL/min, 2% isopropanol, 220 nm) – analysis of 2-phenyl-2-vinylpent-4-en-1-ol (4.86).*



Retention Time	Area	Area %	Height	Height %
23.860	822324844	90.57	15924827	88.91
26.790	85579539	9.43	1987248	11.09
Totals	907904383	100.00	17912075	100.00

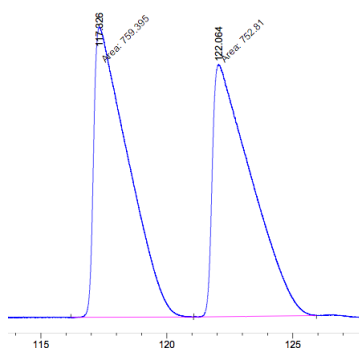


**(S)-(3-methylhexa-1,5-dien-3-yl)cyclohexane (4.57).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 0.87-0.98 (m), 1.20-1.29 (m), 1.62-1.76 (m), 2.10 (2H, d,  $J$  = 7.0 Hz,  $\text{CCH}_2\text{CH}$ ), 4.88 (1H, dd,  $J$  = 17.6, 1.5 Hz,  $\text{CCH}=\text{CH}_a\text{H}_b$ ), 4.96-5.02 (3H, m,  $\text{CCH}=\text{CH}_a\text{H}_b$  &  $\text{CH}_2\text{CHC}=\text{CH}_2$ ), 5.70-5.79 (1H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.75 (1H, dd,  $J$  = 17.6, 8.7 Hz,  $\text{CCH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 19.2, 26.8, 27.1, 27.7, 42.2, 43.3, 45.8, 112.1, 116.5, 135.7, 146.1; IR (neat): 2924.6 (s), 2852.8 (m), 1638.3 (w), 1448.9 (m), 1374.2 (w), 1002.7 (w), 909.9 (m); HMRS (ESI+) for  $\text{C}_{13}\text{H}_{22}$   $[\text{M}+\text{H}]$ : calculated: 179.1805, found: 179.1800;  $[\alpha]_D^{20}$  = +6.9 ( $c$  = 0.96,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica gel (pentane) to afford a colorless oil (23.3 mg, 45% yield), with 7:1 allyl-allyl coupling product to elimination product.  $R_f$  = 0.83 (pentane, stain in  $\text{KMnO}_4$ ).

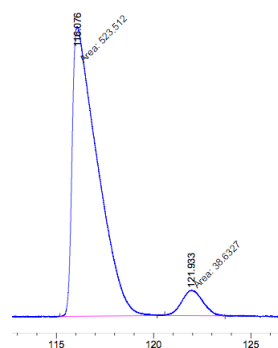
### ***Proof of Stereochemistry:***

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction.

*Chiral GC (CD-GTA, Supelco, 70 °C, 20 psi)-analysis of the title compound.*



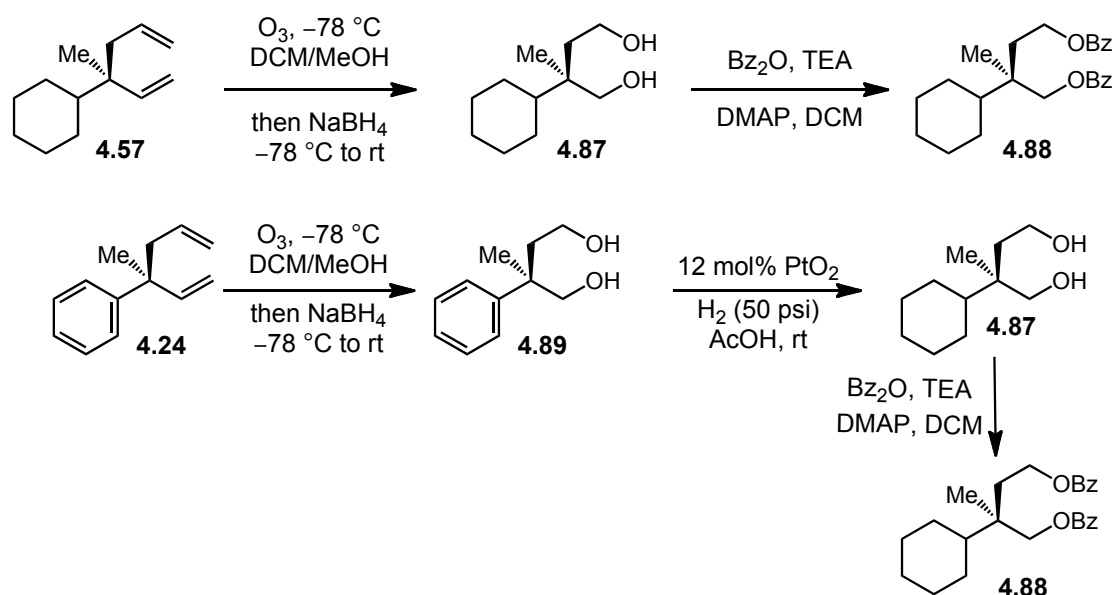
racemic



reaction product

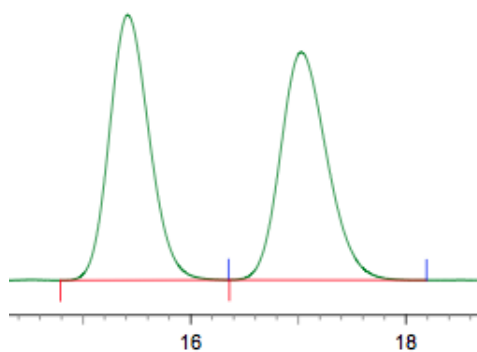
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	116.076	MM	1.4937	523.51239	5.84140	93.12763
2	121.933	MM	1.2522	38.63267	5.14192e-1	6.87237

Absolute stereochemistry was determined by converting the allyl-allyl coupling product to a dibenzoate (**4.89**) by ozonolysis/reduction and dibenzoate protection of the corresponding diol, as shown below. *Via* chiral HPLC, the resulting dibenzoate was compared to the one derived from (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene from ozonolysis/reduction, hydrogenation and dibenzoate protection of the resulting diol, as depicted below.<sup>37</sup>

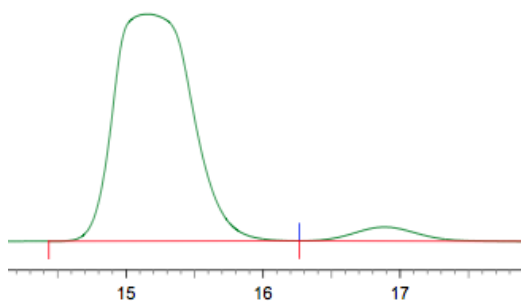


<sup>37</sup> For hydrogenation procedure, see: Hill, R. K.; Cullison, D. A. *J. Am. Chem. Soc.* **1973**, 95, 1229.

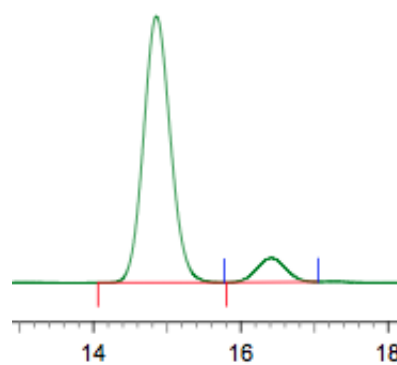
*Chiral HPLC (AD-H, Chirapak, 0.5 mL/min, 2% isopropanol, 220 nm) – analysis of 2-cyclohexyl-2-methylbutane-1,4-diyl dibenzoate (**4.89**).*



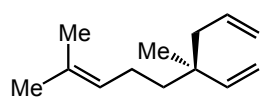
racemic



derived from (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene



derived from reaction product



**(S)-4,8-dimethyl-4-vinylnona-1,7-diene (4.58).**  $^1\text{H}$  NMR (500

MHz,  $\text{CDCl}_3$ ):  $\delta$  0.97 (3H, s,  $\text{CH}_2=\text{CHCCH}_3$ ), 1.26-1.34 (2H, m,

$\text{C}=\text{CHCH}_2\text{CH}_2$ ), 1.58 (3H, s,  $(\text{CH}_3)_a(\text{CH}_3)_b\text{C}=\text{CH}$ ), 1.67 (3H, s,  $(\text{CH}_3)_a(\text{CH}_3)_b\text{C}=\text{CH}$ ),

1.88 (2H, ddd,  $J = 8.5, 8.0, 8.0$  Hz,  $\text{C}=\text{CHCH}_2\text{CH}_2$ ), 2.03-2.19 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ),

4.91 (1H, dd,  $J = 18.0, 1.5$  Hz,  $\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 4.98-5.03 (3H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  &

$\text{CCH}=\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$ ), 5.07-5.10 (1H, m,  $(\text{CH}_3)_2\text{C}=\text{CH}$ ), 5.71-5.80 (2H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$  &

$\text{CCH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.6, 22.7, 22.8, 25.7, 39.5, 40.4, 45.2,

111.7, 116.8, 124.9, 131.1, 135.3, 146.7; IR (neat): 3078.7 (w), 2966.6 (m), 2915.3 (m),

2855.5 (w), 1638.9 (w), 1439.9 (w), 1413.4 (w), 1374.8 (w), 996.4 (m), 910.4 (s), 832.7

(w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{13}\text{H}_{23}$   $[\text{M}+\text{H}]$ : calculated: 179.1800, found: 179.1795;

$[\alpha]_{\text{D}}^{20} = +7.4$  ( $c = 0.97$ ,  $\text{CHCl}_3$ ). The unpurified reaction mixture was purified on silica

gel (pentane) to afford a clear, colorless oil (32.6 mg, 96% yield), with 4:1 allyl-allyl

coupling product to elimination product.  $R_f = 0.81$  (8:1 hexane/EtOAc, stain in  $\text{KMnO}_4$ ).

### ***Proof of Stereochemistry:***

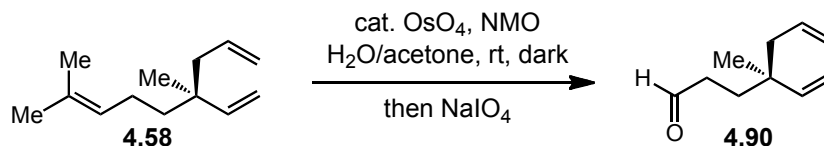
The title compound was subjected to dihydroxylation/cleavage, as depicted below.

The resulting aldehyde (**4.90**) was subjected to chiral GC analysis. The analogous

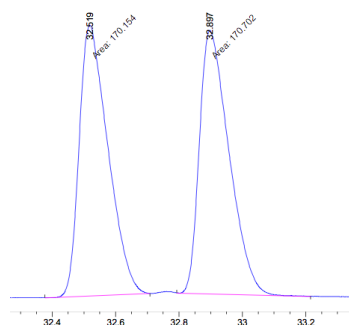
racemic material was prepared *via* the same route through the use of 1,2-

bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction.

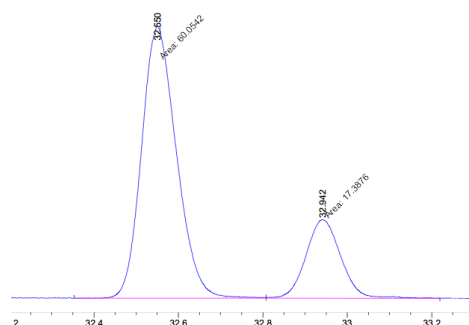
Absolute stereochemistry was assigned by analogy to **4.27**.



Chiral GC ( $\beta$ -dex, Supelco, 60 °C, 10 min, ramp 2 deg/min to 160 °C, 25 psi) - analysis of 4-methyl-4-vinylhept-6-enal (**4.90**).



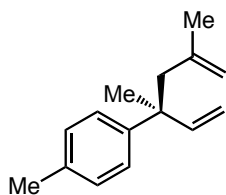
racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.550	MF	0.0952	60.05421	10.51814	77.54754
2	32.942	FM	0.0958	17.38759	3.02506	22.45246





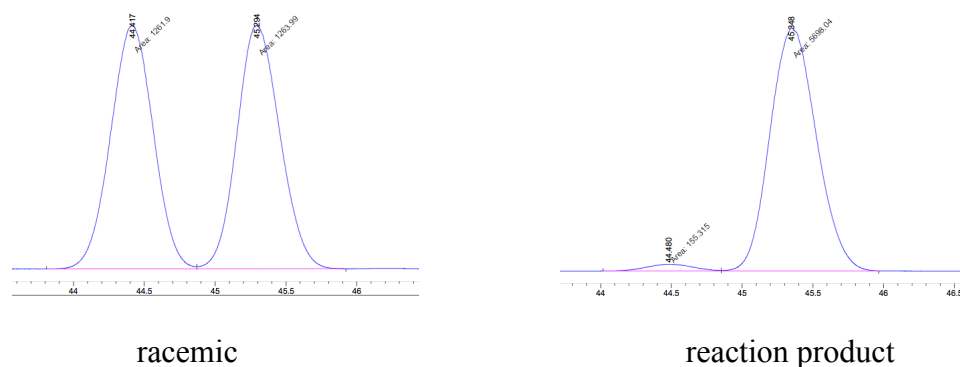
**(R)-1-(3,5-dimethylhexa-1,5-dien-3-yl)-4-methylbenzene (4.66).** <sup>1</sup>H

NMR (500 MHz, CDCl<sub>3</sub>): δ 1.40 (3H, s, ArCCH<sub>3</sub>), 1.43 (3H, s, CH<sub>3</sub>C=CH<sub>2</sub>), 2.32 (3H, s, ArCH<sub>3</sub>), 2.51 (1H, d, *J* = 13.3 Hz, CCH<sub>a</sub>H<sub>b</sub>C), 2.56 (1H, d, *J* = 13.3 Hz, CCH<sub>a</sub>H<sub>b</sub>C), 4.57 (1H, m, CH<sub>3</sub>C=CH<sub>a</sub>H<sub>b</sub>), 4.77 (1H, m, CH<sub>3</sub>C=CH<sub>a</sub>H<sub>b</sub>), 5.01-5.08 (2H, m, CCH=CH<sub>2</sub>), 6.13 (1H, dd, *J* = 17.4, 10.8 Hz, CCH=CH<sub>2</sub>), 7.12 (2H, d, *J* = 7.9 Hz, Ar-H), 7.25 (2H, d, *J* = 8.2 Hz, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 16.1, 19.82, 19.87, 19.93, 19.98, 38.9, 44.8, 106.5, 109.7, 121.8, 123.9, 130.5, 138.4, 139.6, 142.8; IR (neat): 3080.7 (m), 3023.0 (w), 2968.1 (s), 2922.8 (s), 2874.4 (w), 1639.2 (m), 1512.5 (s), 1455.0 (m), 1412.2 (w), 1372.9 (m), 1074.3 (w), 1019.5 (w), 999.8 (w), 912.1 (s), 891.7 (s), 815.1 (s), 734.1 (w), 516.0 (w); HRMS (ESI+) for C<sub>15</sub>H<sub>21</sub> [M+H]<sup>+</sup>: calculated: 201.1643, found: 201.1645; [α]<sub>D</sub><sup>20</sup> = -14.293 (*c* = 0.83, CHCl<sub>3</sub>). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (22.1 mg, 56 % yield), with less than 5% elimination product. *R<sub>f</sub>* = 0.50 (pentane, stain in KMnO<sub>4</sub>).

***Proof of Stereochemistry:***

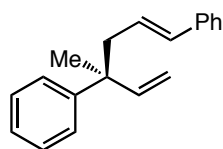
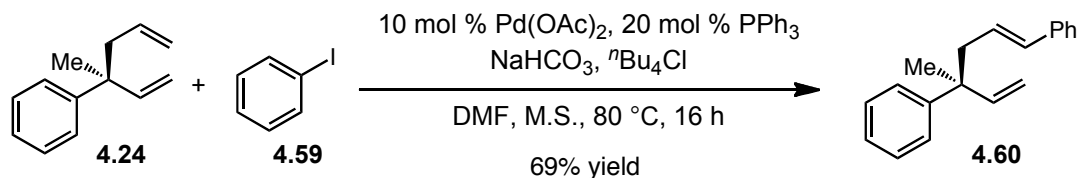
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by converting the title compound to α-cuparenone, as depicted below, and comparing the optical rotation with (+)-α-cuparenone reported by the literature.<sup>32</sup>

*Chiral GC ( $\beta$ -dex, Supelco, 130 °C, 60 min, 20 psi)-analysis of the title compound*




Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	44.480	MF	0.3776	155.31520	6.85529	2.65344
2	45.348	FM	0.3797	5698.03809	250.10944	97.34656

## 7. Functionalization of the Allyl-Allyl Coupling Products



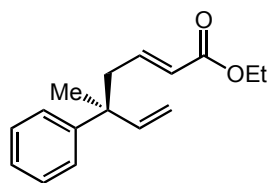
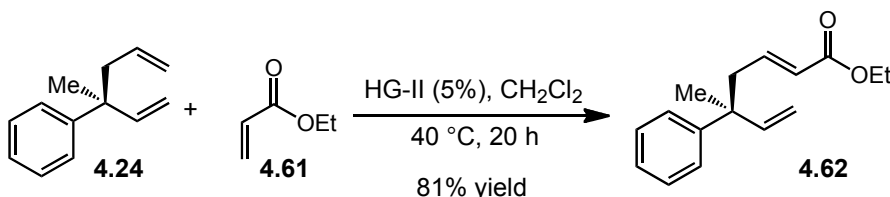
**(*S,E*)-(4-methylhexa-1,5-diene-1,4-diyl)dibenzene (4.60):**<sup>38</sup> To a

 flame-dried 2-dram vial equipped with a stir bar was added powdered molecular sieves (4 Å, 600 mg) and sodium bicarbonate (63.0 mg, 0.750 mmol). The vial was sealed with a septum and purged three times with N<sub>2</sub>. DMF (1.5 mL) was then added by syringe, and the resulting suspension was allowed to stir at room temperature for 15

<sup>38</sup> Jeffery, T. *Tetrahedron* **1996**, 52, 10113.

minutes. The septum was then removed, and triphenylphosphine (15.7 mg, 0.060 mmol) was added all at once to the reaction mixture. The septum was then replaced, and vial was charged with (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (51.6 mg, 0.300 mmol) and iodobenzene (97.9 mg, 0.480 mmol) *via* syringe. The vial was flushed with N<sub>2</sub> for 1 minute. The reaction was allowed to stir for another 15 minutes. The septum was removed again, and Pd(OAc)<sub>2</sub> (6.7 mg, 0.030 mmol) was quickly added all at once followed by immediate sealing with a screw cap. The reaction was heated in an oil bath to 80 °C and allowed to stir for 16 h. The red slurry was then cooled to room temperature and water and Et<sub>2</sub>O were added. The organic layer was transferred out by a pipet and filtered through a plug of silica gel (bottom) and MgSO<sub>4</sub> (top), and the remaining aqueous layer was washed with more ether (3x) and the organics were filtered. The combined organics were concentrated *in vacuo* and purified by silica gel chromatography (100:1 hexanes/EtOAc) to yield a clear, colorless oil (51.8 mg, 70% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.41 (3H, s, CH<sub>3</sub>), 2.66 (1H, dd, *J* = 14.0, 7.0 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CHPh), 2.70 (1H, dd, *J* = 14.0, 7.0 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CHPh), 5.09 (1H, ddd, *J* = 18.0, 1.5, 1.0 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 5.15 (1H, dt, *J* = 10.5, 1.0 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 6.02 (1H, dddd, *J* = 15.5, 8.0, 7.5, 1.5 Hz, CH<sub>2</sub>CH=CHPh), 6.10 (1H, ddd, *J* = 17.5, 11.0, 1.0 Hz, CH=CH<sub>2</sub>), 6.27 (1H, dd, *J* = 15.5, 1.5 Hz, CH<sub>2</sub>CH=CHPh), 7.15-7.26 (6H, m, Ar-H), 7.30-7.37 (4H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 25.1, 44.6, 44.7, 112.2, 125.95, 126.03, 126.6, 126.9, 127.0, 128.1, 128.4, 132.4, 137.7, 146.5, 147.0; IR (neat): 3082.3 (w), 3057.7 (w), 3025.6 (w), 2966.1 (w), 2927.0 (w), 1653.4 (s), 1598.6 (w), 1493.1 (m), 1444.7 (m), 1411.3 (w), 1371.7 (w), 965.2 (s), 908.2 (s), 733.9 (s), 696.5 (s) cm<sup>-1</sup>; HRMS (ESI+) for

C<sub>19</sub>H<sub>21</sub> [M+H]<sup>+</sup>: calculated: 249.1643, found: 249.1649. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -45.3 (*c* = 2.10, CHCl<sub>3</sub>).

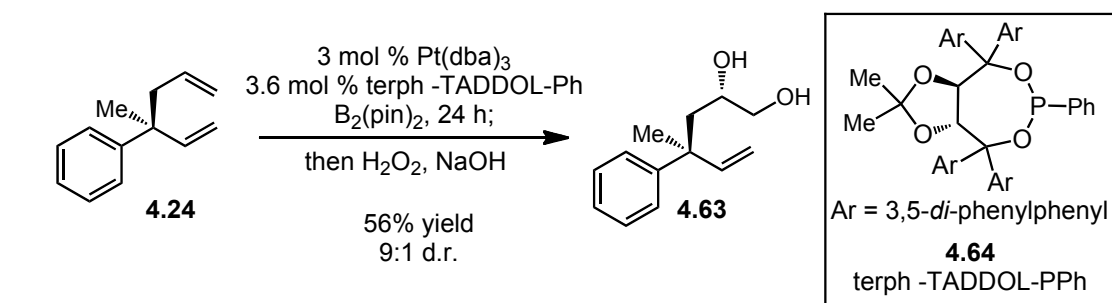


**(*S,E*)-ethyl-5-methyl-5-phenylhepta-2,6-dienoate(4.62).**<sup>39</sup> To an

oven-dried 2-dram screw-cap vial equipped with a stir bar was added (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (64.6 mg, 0.375 mmol), ethyl acrylate (0.12 mL, 1.125 mmol), Hoveyda-Grubbs 2<sup>nd</sup> Generation catalyst (11.9 mg, 0.019 mmol), and methylene chloride (1.5 mL). The vial was then purged for 15 seconds with nitrogen, capped, and sealed with tape. The solution was heated to 40 °C and allowed to stir for 14 h. The solution was then cooled to room temperature and *tert*-butylvinylether (5 drops) was added to the reaction. The resulting solution was allowed to stir at room temperature for 30 minutes. The reaction was then concentrated under reduced pressure and purified by flash chromatography (silica gel, 3% Et<sub>2</sub>O/pentane) to yield a clear, colorless oil (78.7 mg, 86% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.26 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.39 (3H, s, CCH<sub>3</sub>), 2.66 (1H, ddd, *J* = 14.1, 7.6, 1.5 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CHC), 2.70 (1H, ddd, *J* = 14.1, 7.6, 1.5 Hz, CH<sub>a</sub>H<sub>b</sub>CH=CHC), 4.15 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 5.08 (1H, dd, *J* = 17.5, 1.2 Hz, CCH=CH<sub>cis</sub>H<sub>trans</sub>), 5.17 (1H, dd, *J* = 10.8, 1.2 Hz, CCH=CH<sub>cis</sub>H<sub>trans</sub>), 5.82 (1H, ddd, *J* =

<sup>39</sup> BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, 6, 3465.

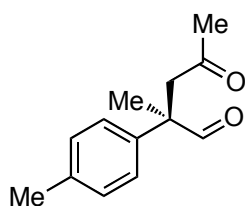
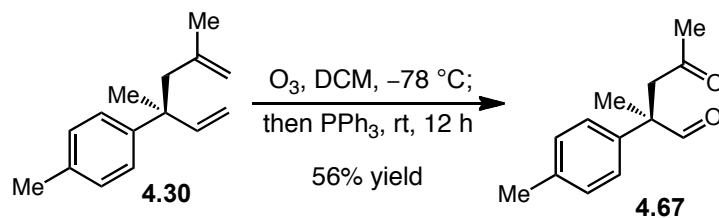
15.7, 1.5, 1.5 Hz, CH<sub>2</sub>CH=CHC), 6.03 (1H, d,  $J$  = 17.5, 10.8 Hz, CCH=CH<sub>2</sub>), 6.78 (1H, ddd,  $J$  = 15.7, 7.6, 7.6 Hz, CH<sub>2</sub>CH=CHC), 7.19-7.23 (1H, m, Ar-H), 7.30-7.33 (4H, m, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.2, 25.2, 43.8, 44.2, 60.2, 112.8, 123.8, 126.2, 126.4, 128.3, 145.6, 146.2 (2C), 166.3; IR (neat): 3085.9 (w), 3057.6 (w), 2978.0 (w), 1719.6 (s), 1653.3 (m), 1494.4 (w), 1445.4 (w), 1412.4 (w), 1310.9 (m), 1264.6 (m), 1155.8 (w), 1096.4 (w), 983.2 (w), 766.4 (w), 700.5 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>16</sub>H<sub>21</sub>O<sub>2</sub> [M+H]: calculated: 245.1542, found: 245.1552.  $[\alpha]_D^{20}$  = -28.519 ( $c$  = 0.23, CHCl<sub>3</sub>).



**(4S)-4-methyl-4-phenylhex-5-ene-1,2-diol (4.63).**<sup>31</sup> In the dry-box an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was charged with Pt(dba)<sub>3</sub> (8.1 mg, 0.009 mmol), 3,5-(*R,R*)-diphenylTADDOLPPh (12.3 mg, 0.010 mmol), B<sub>2</sub>(pin)<sub>2</sub> (77.0 mg, 0.304 mmol) and THF (2.9 mL, 0.1 M). The vial was sealed with a polypropylene cap and removed from the dry-box. The solution was allowed to stir at 80 °C for 30 minutes, at which time the reaction was cooled to room temperature and brought back into the dry-box. (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (50.0 mg, 0.290 mmol) was then added to the reaction

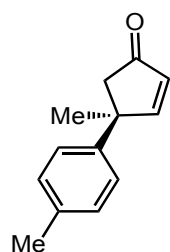
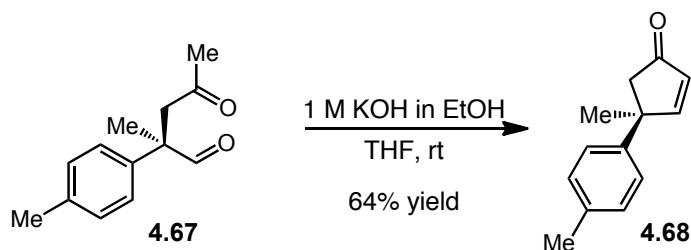
mixture. The vial was again sealed and removed from the dry-box. The reaction was heated to 60 °C and allowed to stir for 24 h. The reaction was then cooled to 0 °C (ice-water bath) and charged with 3 M NaOH (2 mL) and 30% H<sub>2</sub>O<sub>2</sub> (w/w) (1 mL). The resulting mixture was allowed to stir for 4 h while slowly warming to room temperature. The mixture was again cooled to 0 °C (ice-water bath) and quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL), added drop-wise *via* syringe. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by flash chromatography (silica gel, 1:1 pentane/EtOAc) to afford a clear, pale yellow oil (57.9 mg, 56% yield of title compound), with 1:1.3 desired product to pinacol. *R*<sub>f</sub> = 0.28 (2:3 hexanes/EtOAc, stain in KMnO<sub>4</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.48 (s, 3H, CH<sub>3</sub>), 1.91 (2H, d, *J* = 5.4 Hz, CH<sub>2</sub>CHOH), 2.24-2.72 (2H, m, 2(OH)), 3.31 (1H, dd, *J* = 11.1, 7.8 Hz, CH<sub>a</sub>H<sub>b</sub>OH), 3.39 (1H, dd, *J* = 11.1, 3.2 Hz, CH<sub>a</sub>H<sub>b</sub>OH), 3.66-3.70 (1H, m, CH<sub>2</sub>CHOH), 5.10 (1H, d, *J* = 17.6 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 5.14 (1H, d, *J* = 10.9 Hz, CH=CH<sub>cis</sub>H<sub>trans</sub>), 6.14 (1H, dd, *J* = 17.6, 10.9 Hz, CH=CH<sub>2</sub>), 7.18-7.21 (1H, m, Ar-H), 7.29-7.35 (4H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 24.8, 43.5, 44.2, 67.3, 69.6, 112.1, 126.2, 126.5, 128.3, 146.7, 147.1; IR (neat): 3364.9 (br, s), 3058.0 (w), 2973.9 (w), 2931.9 (w), 1634.4 (w), 1599.6 (w), 1444.7 (m), 1373.0 (m), 1154.3 (m), 1096.5 (m), 1061.5 (s), 1001.7 (m), 912.8 (s), 764.2 (s), 698.9 (s) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>13</sub>H<sub>19</sub>O<sub>2</sub> [M+H]: calculated: 207.1385, found: 207.1395. [α]<sub>D</sub><sup>20</sup> = +35.2 (*c* = 0.52, CHCl<sub>3</sub>).

## 8. Synthesis of (+)- $\alpha$ -Cuparenone



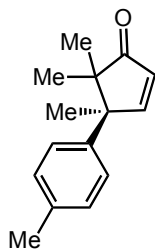
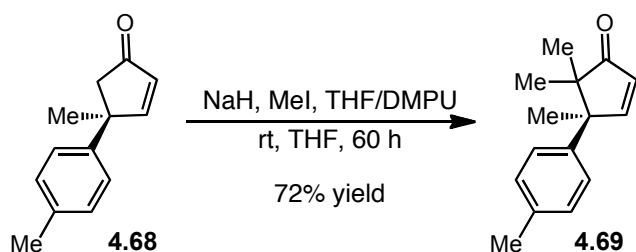
**(R)-2-methyl-4-oxo-2-*p*-tolylpentanal (4.67).** To a round-bottom flask equipped with a stir bar was added (*S*)-1-(3,5-dimethylhexa-1,5-dien-3-yl)-4-methylbenzene (60.0 mg, 0.30 mmol) and CH<sub>2</sub>Cl<sub>2</sub>

(15 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$ . O<sub>3</sub> gas was bubbled through the solution until a light blue color appeared. N<sub>2</sub> was re-introduced into the flask to remove excess O<sub>3</sub>. When the solution went colorless, PPh<sub>3</sub> (393 mg, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added at once. The solution was warmed to room temperature and stirred under N<sub>2</sub> overnight. Solvent was removed *in vacuo*. The residue was purified by flash chromatography with hexanes/Et<sub>2</sub>O (4:1) to afford (*R*)-2-methyl-4-oxo-2-*p*-tolylpentanal as a yellow oil (33.5 mg, 56% yield). Spectral data is in accordance with literature.<sup>32</sup>



**(S)-4-methyl-4-*p*-tolylcyclopent-2-enone (4.68):**<sup>40</sup> To a round-bottom flask equipped with a stir bar was added (*R*)-2-methyl-4-oxo-2-*p*-tolylpentanal (109.4 mg, 0.53 mmol), 1M KOH in EtOH (0.53 ml, 0.53 mmol), and THF (10 mL). The resulting solution was allowed to stir for 1

h. Solvent was evaporated *in vacuo*, and the remaining residue was purified flash chromatography with hexanes/Et<sub>2</sub>O (20:1 to 2:1) to afford (*S*)-4-methyl-4-*p*-tolylcyclopent-2-enone as a colorless oil (62.7 mg, 70% yield). Spectral data is in accordance with literature.<sup>32</sup>

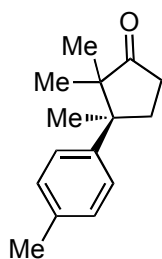
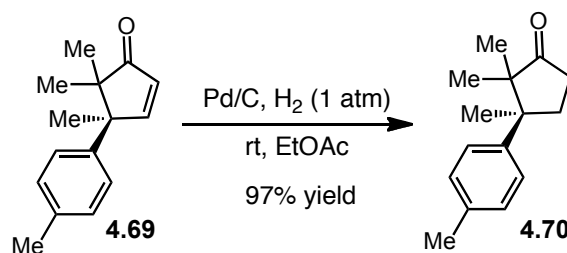


**(S)-4,5,5-trimethyl-4-*p*-tolylcyclopent-2-enone (4.69).** To a flame-dried flask equipped with a stir bar and charged with NaH (12 mg, 0.50 mmol) was added (*S*)-4-methyl-4-*p*-tolylcyclopent-2-enone (11.6 mg, 0.05 mmol), THF (0.75 mL) and DMBU (0.25 mL). The suspension was allowed to stir

<sup>40</sup> Procedure adapted from previously reported conditions: Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 6, 1441.



for 1 h followed by the addition of MeI (31  $\mu$ L, 0.50 mmol). The resulting suspension was allowed to stir for 60 h at room temperature. MeOH (1 mL) was added to quench excess NaH; and volatiles were removed *in vacuo*. The resulting yellow residue was dissolved in diethyl ether and was washed with H<sub>2</sub>O. The organic extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting oil was purified by flash chromatography with hexanes/Et<sub>2</sub>O (4:1) to afford (*S*)-4,5,5-trimethyl-4-*p*-tolylcyclopent-2-enone as a colorless oil (9.6 mg, 72% yield).<sup>40</sup> Spectral data is in accordance with literature.<sup>32</sup>



**(+)- $\alpha$ -cuparenone (4.70).** To a round-bottom flask equipped with a stir bar and charged with (*S*)-4,5,5-trimethyl-4-*p*-tolylcyclopent-2-enone (9.5 mg, 0.044 mmol) and Pd/C (4.7 mg, 10 mol %) was added EtOAc (1.0 mL). H<sub>2</sub> atmosphere (1 atm) was introduced. The solution was allowed to stir for 2 h at room temperature, then filtered over celite. The residue upon solvent evaporation *in vacuo* was purified by flash chromatography with hexane/Et<sub>2</sub>O (9:1) to yield (+)- $\alpha$ -cuparenone (8.3 mg, 93% yield).<sup>40</sup> Spectral data is in accordance with literature.<sup>32</sup>  $[\alpha]_{\text{D}}^{20} = +170$  ( $c = 0.14$ , CHCl<sub>3</sub>).

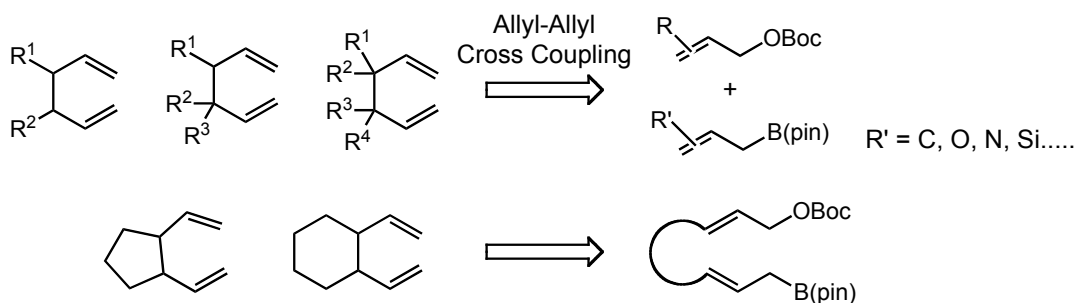
## Chapter V

### Nickel- and Palladium-Catalyzed Highly Efficient and Convenient Synthesis of Substituted and Functionalized Allylic Boronates

#### I. INTRODUCTION

The palladium-catalyzed allyl-allyl cross-coupling enables the regio- and enantioselective assembly of 1,5-dienes bearing tertiary and quaternary centers, as described in chapters III and IV. The further development of this method for the construction of more sophisticated 1,5-dienes, such as those containing contiguous stereogenic centers and cyclic-diene moieties (Scheme 5.1), is dependent upon the easy access to the substituted and functionalized allylic boronate building blocks. Therefore, efforts were undertaken to develop efficient and convenient methods to synthesize the allyl metal reagents from readily available and inexpensive starting materials.

Scheme 5.1



## II. BACKGROUND

Due to the importance of allylic boronates in synthetic organic chemistry, their synthesis has been widely studied. Transmetalation of allyl metals, such as allyllithiums,<sup>1</sup> allylmagnesiums,<sup>2</sup> allylpotassiums,<sup>3</sup> or allyltins<sup>4</sup> to boron was used extensively for the generation of allylboron reagents. Homologation<sup>5</sup> of vinylboronates also delivers allylic boronates and has the ability to insert multiple carbon tethers and introduce stereogenic centers. The use of strongly basic reagents in above methods, however, substantially limits their application in the synthesis of multifunctional allylic boronates.

Since transition metals are capable of both cleaving and creating carbon-metal bonds, synthesis of allylborates employing catalytic amount of transition metals has also been studied as it offers higher atom-economy and milder conditions. Catalytic regioselective diboration of 1,3-dienes<sup>6</sup> and allenes,<sup>7</sup> for example, have been demonstrated for the conversion of simple hydrocarbons to functionalized organoboron building blocks. With suitable chiral ligands, enantiomerically-enriched allylic

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<sup>1</sup> For representative examples: Brown, H. C.; Rangaishenvi, M. V. *Tetra. Lett.* **1990**, 31, 7113.

<sup>2</sup> For representative examples: (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, 107, 8186. (b) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, 55, 1868.

<sup>3</sup> For representative examples: Hoffmann, R. W.; Zeiss, H. *J. Org. Chem.* **1981**, 46, 1309.

<sup>4</sup> For representative examples: Hoffman, R.W.; Feussner, G.; Zeiss, H.; Schultz, S. *J. Organomet. Chem.* **1980**, 187, 321.

<sup>5</sup> For representative examples: (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, 102, 7588. (b) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, 4, 1687. (c) Brown, H. B.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, 51, 3150. (d) Althaus, M.; Mahmmod, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, 132, 4025.

<sup>6</sup> For representative examples: (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073. (b) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, 5, 2573. (c) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, 131, 9134.

<sup>7</sup> For representative examples: (a) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, 39, 2357. (b) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, 3, 271. (c) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, 125, 8702. (d) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, 126, 16328. (e) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, 129, 8766.

boronates<sup>6c, 7c-e</sup> can be synthesized. Likewise, regioselective hydroboration of 1,3-dienes catalyzed by Pd,<sup>8a</sup> Rh,<sup>8a</sup> Fe,<sup>8b</sup> or Ni<sup>8c</sup> yields cyclic and acyclic allylic boronates. Recently, cross metathesis<sup>9</sup> between simple allylboronates containing terminal or internal alkenes was reported. This reaction facilitates construction of functionalized and substituted allylic boronates by forming new carbon-carbon bonds, although *E/Z* selectivity needs to be further improved.

Allylic electrophiles have long been used as versatile substrates in transition metal catalyzed cross coupling or substitution reactions. The preparation of allylic boronates through the cross coupling between boron nucleophiles and allylic electrophiles was pioneered by Miyaura and co-workers.

Under mild and neutral reaction conditions, Miyaura showed that Pd(dba)<sub>2</sub> could catalyze the C-B bond formation between allylic acetates and bis(pinacolato)diboron [**5.1**, B<sub>2</sub>(pin)<sub>2</sub>], with high regio- and stereoselectivity (Scheme 5.2).<sup>10</sup> This cross coupling is proposed to start with oxidative addition of the allylic acetate to Pd(0) and leads to a Pd- $\pi$ -allyl complex (**5.I**, Scheme 5.2); transmetallation with B<sub>2</sub>(pin)<sub>2</sub> and reductive elimination of the resulting complex (**5.II**) at the less sterically demanding site to afford the linear product. Allyl-allyl dimerization is occasionally observed, and was found to be dependent on the leaving group, with carbonates generating the most 1,5-diene byproducts. The preference of borylation over dimerization suggests the transmetallation

<sup>8</sup> For representative examples: **Pd and Rh**: (a) Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1989**, 30, 3789. **Fe**: (b) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, 131, 12915. **Ni**: (c) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, 132, 2534.

<sup>9</sup> For representative examples: (a) Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128. (b) Dolman, S. J.; Hultzs, K. C.; Pezet, F.; Teng, X.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2004**, 126, 10945.

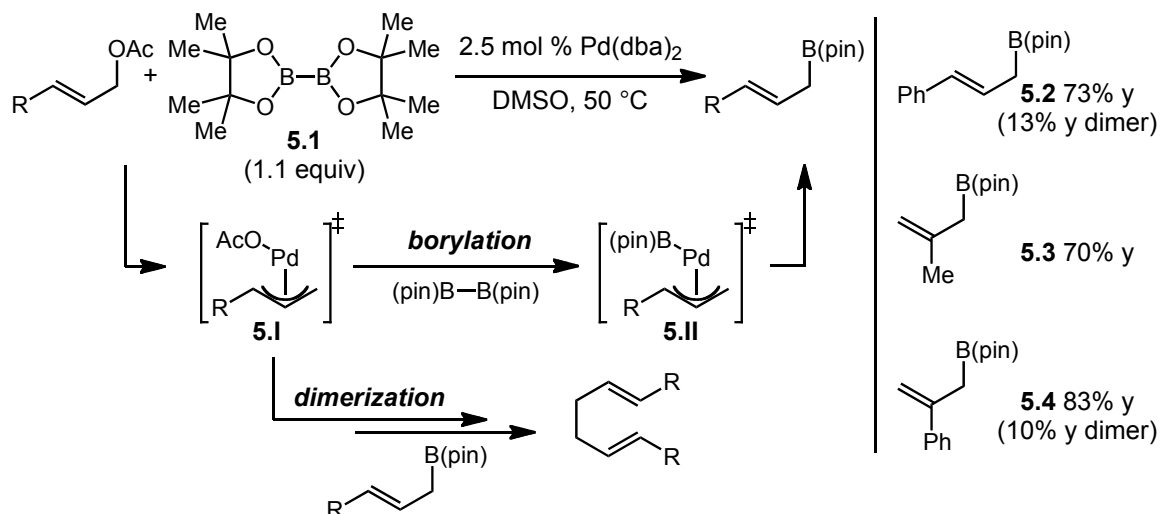
<sup>10</sup> Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, 37, 6889.

of **5.I** with diboron (**5.1**) is faster than the reaction with the allylboron coupling partner (e.g. **5.2**). When carbonates serve as leaving groups, however, the strong nucleophilic alkoxides (generated from the decomposition of carbonates) appear to activate the allylboron more effectively and facilitate dimerization. *E* alkenes are always observed in the products, consistent with a hypothesis that coupling reactions involve Pd- $\pi$ -allyl complexes as an intermediate, regardless of the isomeric forms of the substrates. Miyaura noted that decomposition of the catalyst and resulting precipitation of palladium black at the early stage of the reaction cause low conversion of starting materials in solvents such as benzene or DMF, but was found to be minimal when DMSO was employed in the reaction, resulting in the best catalytic activity. Due to the readily available substrates and catalyst, Miyaura borylation is widely used for the synthesis of sophisticated allylboron reagents.<sup>11</sup> Regrettably, the dimerization of substrates and the use of DMSO as solvent can be considered as limiting factors for this method in a practical application.

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<sup>11</sup> For the applications of Miyaura borylation: (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807. (b) Vogt, M.; Ceylan, S.; Kirshning, A. *Tetrahedron* **2010**, *66*, 6450.

**Scheme 5.2**

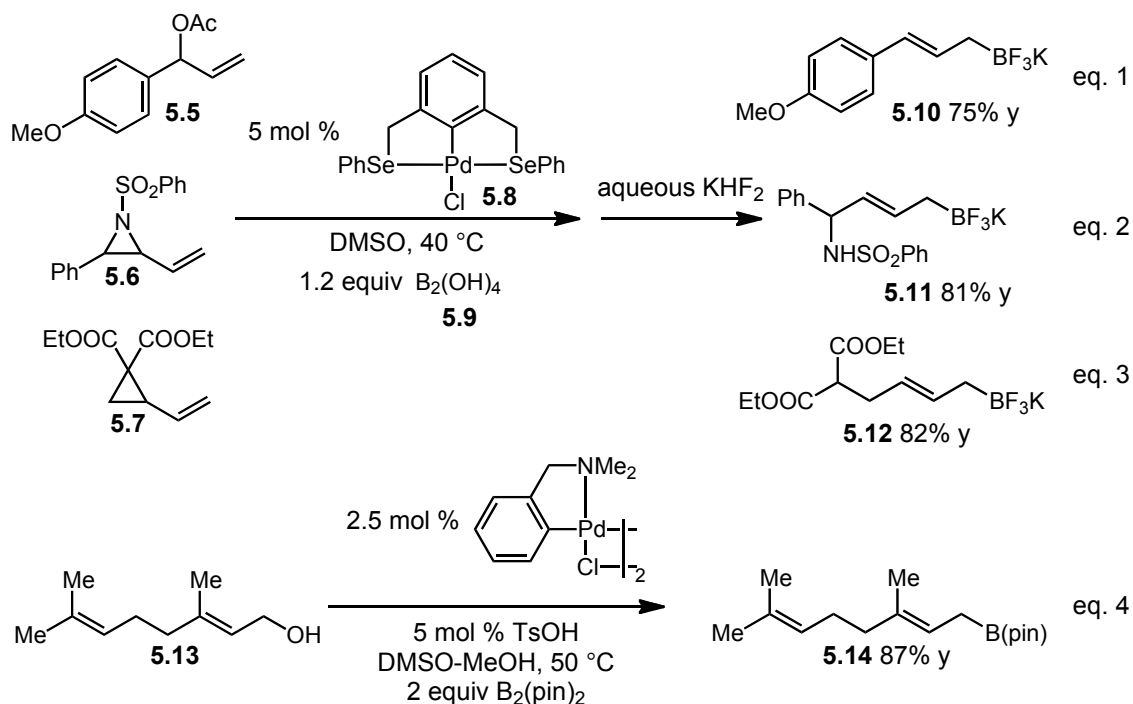


Szabó and co-workers later reported that a Pd pincer complex catalyzes boron transfer reactions from tetrahydroxydiboron (**5.9**) to functionalized allylic acetates, vinyl aziridines and vinyl cyclopropanes (Equations 1-3, Scheme 5.3).<sup>12</sup> These reactions overcome the dimerization of substrates, delivering allylic boronic acids with high efficiency and selectivity. These products subsequently react with aqueous  $\text{KHF}_2$  to obtain the corresponding stable trifluoro(allyl)borates. This method was further optimized to directly couple allylic alcohols with  $\text{B}_2(\text{pin})_2$  (**5.1**), generating stable allylic boronic esters in a single step (Equation 4, Scheme 5.3).<sup>13</sup> TsOH was used as a co-catalyst, which is believed to promote the formation of the boron-activated allylic alcohols through a transesterification process. The use of these methods so far is still quite limited due to the use of specialized catalysts and the use of high boiling point solvents (DMSO-MeOH).

<sup>12</sup> Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478.

<sup>13</sup> Dutheuil, G.; Selander, N.; Szabó, K. J. Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293.

### Scheme 5.3

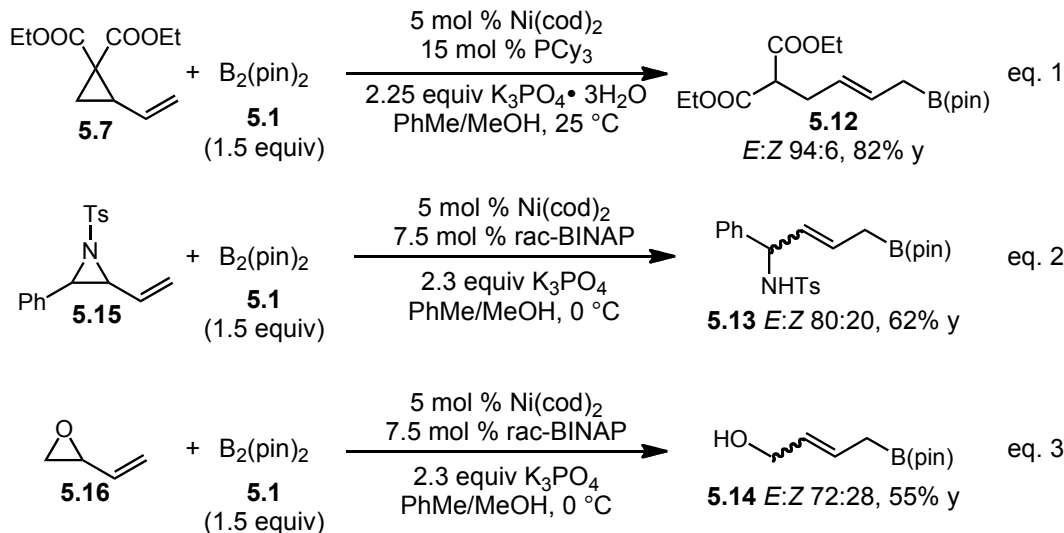


Ni has also been employed for the borylative ring opening reactions of vinyl cyclopropanes,<sup>14</sup> vinyl epoxides<sup>15</sup> and aziridines<sup>15</sup> with  $B_2(pin)_2$  (**5.1**), which provide functionalized allylic boron reagents (Scheme 5.4). These Ni-catalyzed transformations require the addition of base and create allylborates with lower *E*-selectivity of the alkenes compared to the Pd-catalyzed reactions.

<sup>14</sup> Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4677.

<sup>15</sup> Crotti, S.; Bertolini, F.; Macchia, F.; Pineschi, M. *Org. Lett.* **2009**, *11*, 3762.

#### Scheme 5.4



In a complementary fashion, Masuda described a Pt-catalyzed carbon-boron bond formation between allylic electrophiles and boron nucleophiles and realized a somewhat surprising reaction: the coupling between allylhalides and pinacolborane under basic conditions affords allylboron products.<sup>16</sup> More understanding of the mechanistic aspects is needed.

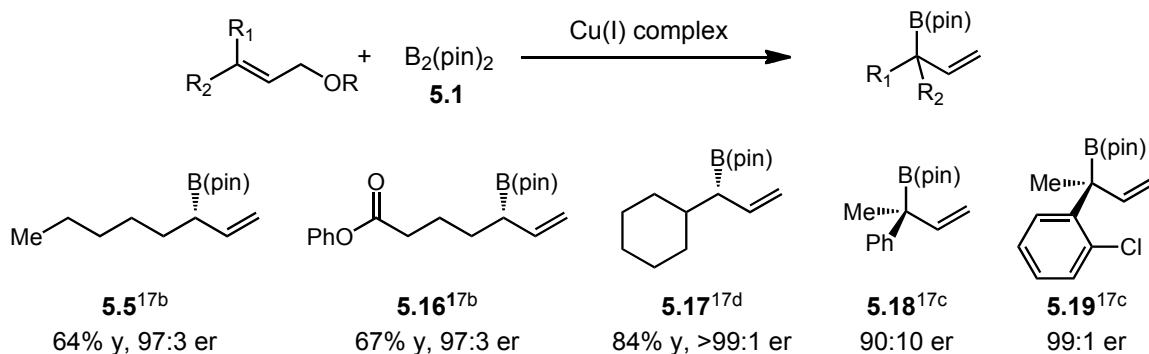
The allylboron reagents can also be synthesized through a  $\gamma$ -selective and stereospecific allylic borylation, which allows easy access to functionalized and/or optically active building blocks. Preliminary investigations revealed that Cu(I) complexes are able to catalyze such transformations, and with suitable chiral ligands, secondary and tertiary allylic boronates can be synthesized with high enantiopurity from corresponding

<sup>16</sup> Murata, M.; Watanabe, S.; Masuda, Y. *Tetra. Lett.* **2000**, 41, 5877.



allyl alcohol derivatives.<sup>17</sup> The addition of nucleophilic Cu(I)-B(pin) intermediate to the allylic electrophile<sup>17a-c</sup> is believed to be the key transformation in the catalytic cycle; however, in some cases a Cu- $\pi$ -allyl complex is suspected to be involved<sup>17d</sup> where isomerically pure substrates are not required.

### Scheme 5.5



During the development of allyl-allyl cross-coupling in the Morken group, we realized that the readily availability and simple synthesis of the functionalized and substituted allyl metal starting materials was crucial for continued studies. The ideal synthesis of allylic boronates to us, should include the following features: (1) use commercially available metal sources and readily available electrophiles, (2) avoid using reagents in excess to reduce costs and simplify purification, (3) anticipate a potential borylation/cross-coupling one-pot procedure, by taking advantage of reaction conditions (e.g. metal catalyst, solvent) such that a second cross-coupling would proceed smoothly upon the addition of another electrophile, (4) develop reactions that allow easy isolation

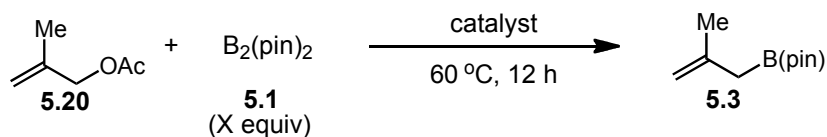
<sup>17</sup> (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (c) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634. (d) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410.

of products (volatile solvents, removable by products). Hence, we began studying the allylic borylation with the hopes of developing highly practical and efficient methods for the direct construction of allylic boronate building blocks.

### III. NICKEL- AND PALLADIUM- CATALYZED ALLYLIC BORYLATION

**A. Modification of Original Miyaura Conditions.** As illustrated in entry 2, Table 5.1, the original Miyaura conditions (entry 1) were first modified by through the use of only 1 equivalent of  $B_2(\text{pin})_2$  and employing THF as solvent (*vs* DMSO). Such changes dramatically diminished the catalyst activity: less than 5% (*vs* 100% in entry 1) of the substrate was converted after a 12-hour reaction time at 60 °C. Several strategies were applied to improve the reactivity of the Pd-catalyzed allylic borylation. Additives that are known to promote coupling reactions involving boronate nucleophiles were examined in this transformation, and indeed, both  $Cs_2CO_3$  and CsF proved beneficial in a concentration dependent manner. However these additives were not effective enough to deliver methallylB(pin) (**5.3**) with full conversion (entries 4-8). Further evaluation of different palladium sources and solvents uncovered another promising feature. Good conversion (73%) of 2-methylallylacetate (**5.20**) was observed when  $Pd(OAc)_2$  was used as the catalyst and toluene as the solvent. Because the starting acetates and allylic boronates share very similar polarities on silica gel, achieving full consumption of starting material is critical for the ease of purification and thus high yield of the product. Therefore, a reaction condition that promotes the full-conversion of substrate needed to be uncovered.

**Table 5.1 Modification of Miyaura Condition.**



entry	catalyst	additive	X	solvent	%conv. <sup>a</sup> (%yield <sup>b</sup> )
1	2.5 mol % $Pd_2(\text{dba})_3$	none	1.1	DMSO [0.16 M]	100 (62)
2	5 mol % $Pd_2(\text{dba})_3$	none	1	THF [0.5 M]	<5
3	5 mol % $Pd_2(\text{dba})_3/\text{dppBz}$	none	1	THF [0.5 M]	<5
4	5 mol % $Pd_2(\text{dba})_3$	1.2 equiv $Cs_2CO_3$	1	THF [0.5 M]	56
5	5 mol % $Pd_2(\text{dba})_3$	1.2 equiv CsF	1	THF [0.5 M]	12
6	5 mol % $Pd_2(\text{dba})_3$	3 equiv $Cs_2CO_3$	1	THF [0.5 M]	84
7	5 mol % $Pd_2(\text{dba})_3$	3 equiv $Cs_2CO_3$	1	PhMe [0.5 M]	52
8	5 mol % $Pd_2(\text{dba})_3$	3 equiv $Cs_2CO_3$	1	EtOAc [0.5 M]	90
9	10 mol % $Pd(\text{OAc})_2$	none	1	THF [0.5 M]	4
10	10 mol % $Pd(\text{OAc})_2$	none	1	PhMe [0.5 M]	73
11	10 mol % $Pd(\text{OAc})_2$	none	1	EtOAc [0.5 M]	13
12	10 mol % $Pd(\text{OAc})_2$	3 equiv $Cs_2CO_3$	1	THF [0.5 M]	29
13	10 mol % $Pd(\text{OAc})_2$	3 equiv $Cs_2CO_3$	1	PhMe [0.5 M]	5
14	10 mol % $Pd(\text{OAc})_2$	3 equiv $Cs_2CO_3$	1	EtOAc [0.5 M]	11

<sup>a</sup> Conversion determined by  $^1\text{H}$  NMR analysis of unpurified reaction mixture. <sup>b</sup> Yields of purified products.

**B. The Ni-Catalyzed Allylic Borylation.** Inspired by the work from Oshima<sup>14</sup> and Pineschi<sup>15</sup>, in which Ni/phosphine complexes catalyze the carbon-boron bond formation between vinyl propanes, vinyl epoxides or vinyl aziridines with diboron reagents, we began to investigate the Ni-catalyzed allylic borylative coupling between allyl acetates with  $B_2(\text{pin})_2$ . To our delight, by using 1:1 mixture of  $Ni(\text{cod})_2$  and  $PPh_3$  as

catalyst, 2-methylallylacetate (**5.20**) can be fully converted to the desired methallylB(pin) (**5.3**) in THF, after a 12-hour reaction time (entry 2, Table 5.2). Notably, compared to Ni-catalyzed borylations pioneered by Oshima and Pineschi, no base is necessary in this reaction, presumably due to the activation of B<sub>2</sub>(pin)<sub>2</sub> by the acetate leaving group. Impressively, relatively less toxic solvent EtOAc exhibits equal catalyst activity, with which, 60% yield of allylboron compound was isolated out of a full-conversion reaction (entry 3). However, this product is contaminated by roughly 5% PPh<sub>3</sub>, confirmed by <sup>1</sup>H NMR and mass spectroscopy analysis. Replacing PPh<sub>3</sub> with more electron rich PCy<sub>3</sub> affords pure metallylB(pin) (**5.3**) in excellent yield and due to the rapid oxidation of the latter ligand on work-up, it is much easier to be removed by chromatography than PPh<sub>3</sub> (entry 6).

**Table 5.2 Condition Optimization for Ni-Catalyzed Allylic Borylation**

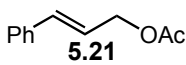
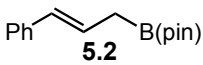
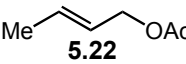
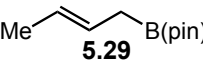
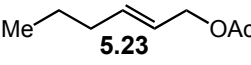
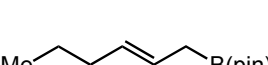
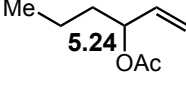
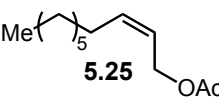
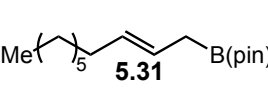
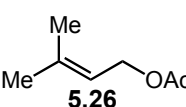
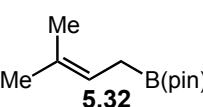
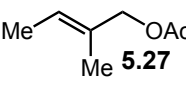
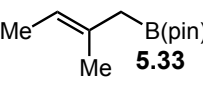
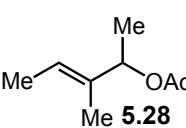
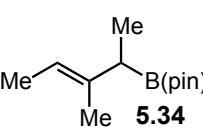
entry	catalyst	solvent	temp.	%conv. <sup>a</sup> (%yield <sup>b</sup> )
1	10 mol % Ni(cod) <sub>2</sub>	THF	60 °C	75
2	10 mol % Ni(cod) <sub>2</sub> /PPh <sub>3</sub> <sup>d</sup>	THF	60 °C	100
3	10 mol % Ni(cod) <sub>2</sub> /PPh <sub>3</sub> <sup>d</sup>	EtOAc	60 °C	100 (60 <sup>c</sup> )
4	10 mol % Ni(cod) <sub>2</sub> /PPh <sub>3</sub> <sup>d</sup>	EtOAc	rt	92
5	5 mol % Ni(cod) <sub>2</sub> /PPh <sub>3</sub> <sup>d</sup>	EtOAc	60 °C	100 (84 <sup>c</sup> )
6	5 mol % Ni(cod) <sub>2</sub> /PCy <sub>3</sub> <sup>d</sup>	EtOAc	60 °C	100 (80)
7	10 mol % Ni(cod) <sub>2</sub>	EtOAc	60 °C	53

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR analysis of unpurified reaction mixture. <sup>b</sup> Yields of purified products. <sup>c</sup> The purified product is contaminated by PPh<sub>3</sub>. <sup>d</sup> The metal:ligand ratio is 1:1.

With the identification of optimal conditions, a series of allylic acetates was subjected to the borylation in EtOAc through the use of a  $\text{Ni}(\text{cod})_2/\text{PCy}_3$  catalyst system. As illustrated in Table 5.3, a good level of substitution was tolerated, generally delivering terminal allylic boronate products with excellent *E*-selectivity. Internal and terminal allylacetates, regardless of isomeric forms, can be used interchangeably in this reaction. Both aromatic (entry 1) and simple aliphatic (entries 2-5) substrates proceed with good yield. Substrates with more complex substitution patterns (e.g. **5.26**, **5.27** and **5.28**) also react smoothly and form the C-B bond at the less sterically hindered site.

**Table 5.3 Substrate Scope in the Ni-Catalyzed Allylic Borylation**

$$\text{R}-\text{CH}=\text{CH}-\text{CH}_2-\text{OAc} \xrightarrow[\text{1.0 equiv B}_2(\text{pin})_2]{\text{5 mol \% Ni(cod)}_2, \text{5 mol \% PCy}_3, \text{EtOAc, 60 }^\circ\text{C, 12 h}} \text{R}-\text{CH}=\text{CH}-\text{CH}_2-\text{B}(\text{pin})$$

entry	substrate	product	%yield <sup>a</sup>
1	 <b>5.21</b>	 <b>5.2</b>	92
2	 <b>5.22</b>	 <b>5.29</b>	84 <sup>b</sup>
3	 <b>5.23</b>	 <b>5.30</b>	94
4	 <b>5.24</b>		96
5	 <b>5.25</b>	 <b>5.31</b>	92
6	 <b>5.26</b>	 <b>5.32</b>	93% <sup>b</sup>
7	 <b>5.27</b>	 <b>5.33</b>	60% <sup>b</sup>
8	 <b>5.28</b>	 <b>5.34</b>	94% <sup>b</sup>

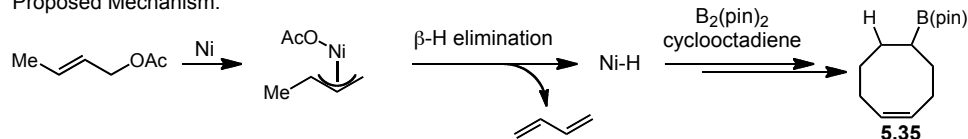
<sup>a</sup> Yields of purified products. <sup>b</sup> 3~10% impurity.

Notice in the last three entries as well as in entry 2, an unknown compound is inseparable from the desired allylic boronates (no more than 10%), which appears to be

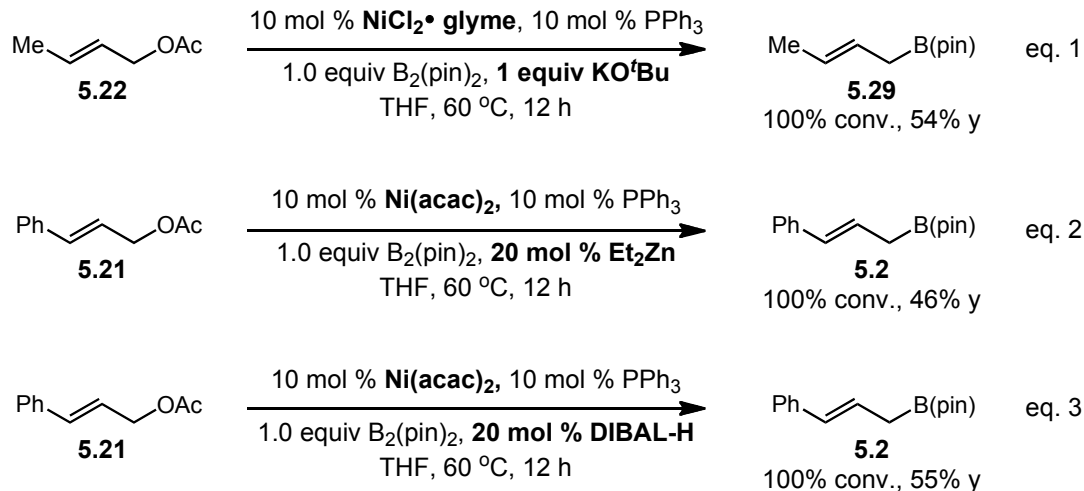
derived from the monohydroboration of 1,5-cyclooctadiene (cod).<sup>18</sup> Although the allylboron reagents could still be utilized in subsequent transformations such as allylboration, efforts were taken to minimize the formation of impurity **5.35** thus obtaining pure products. It was anticipated that the use of nickel sources without cod would exclude the substrate for the hydroboration, based upon the above hypothesis. While Ni(PPh<sub>3</sub>)<sub>4</sub> was completely inactive and failed to produce any allylborate products, we anticipated reducing Ni(II) to Ni(0) *in situ*, allowing for the use of more air- and moisture stable Ni(II) precursors. Among a panel of Ni(II) sources, ligands and bases examined in the Ni-catalyzed allylic borylation of allylacetates, we were able to realize a few of promising conditions, under which pure products were isolated out of fully converted reactions. As shown in Scheme 5.6, NiCl<sub>2</sub>•glyme and Ni(acac)<sub>2</sub> are suitable Ni(II) sources with KO<sup>t</sup>Bu (reduction presumably requires B<sub>2</sub>(pin)<sub>2</sub>), Et<sub>2</sub>Zn, DIBAL-H as the most encouraging reducing reagents. As expected, the appearance of the previously mentioned by-product is no longer observed, however, in general the yields of the allylboron products were lower and the catalyst loading was higher under the new sets of conditions.

<sup>18</sup> This impurity is inseparable from the desired products. The <sup>1</sup>H NMR spectra of the isolated mixtures were compared to the reported <sup>1</sup>H NMR spectrum of **5.35**: Villa, G.; Povie, G.; Renaud, P. *J. Am. Chem. Soc.* **2011**, *133*, 5913.

Proposed Mechanism:



### Scheme 5.6



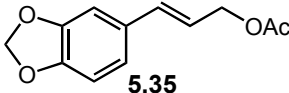
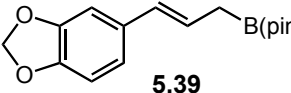
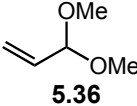
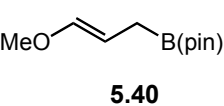
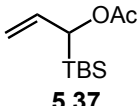
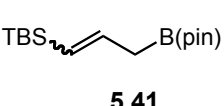
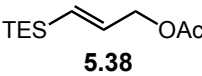
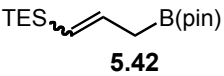
As shown in Table 5.4, functionalized, synthetically useful allylic boronates are synthesized easily using the Ni-catalyzed allylic borylation. Oxygenated aromatic ring (**5.35**) functionality is well tolerated. More impressively, allylboron compounds bearing oxygen (**5.40**) and silyl (**5.41** and **5.42**) substituents on the  $\gamma$ -carbon can also be generated from readily available allylic acetates or vinyl acetals in good to excellent yield. Compared to the previously reported optimal route towards (*E*)- $\gamma$ -methoxyallylborate (**5.40**), which requires the hydroboration of an alkyne followed by an Ir-catalyzed alkene isomerization of the corresponding 1-alkenylboronate, entry 2 in Table 5.4 represents a significant advance.<sup>19</sup>

<sup>19</sup> Moriya, T.; Suzuki, A.; Miyaoura, N. *Tetra. Lett.* **1995**, 36, 1887.



**Table 5.4 The Syntheses of Functionalized Allylborates**

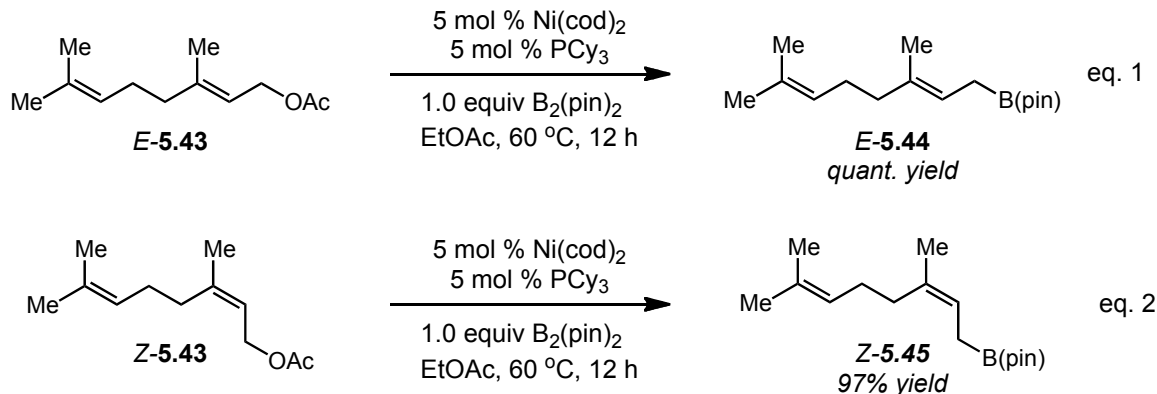
$$\begin{array}{c}
 \text{5 mol \% Ni(cod)}_2, \text{ 5 mol \% PCy}_3 \\
 \text{EtOAc, 60 } ^\circ\text{C, 12 h} \\
 \text{1.0 equiv B}_2(\text{pin})_2
 \end{array}
 \xrightarrow{\hspace{1cm}}$$

entry	substrate	product	%yield <sup>a</sup>
1	 <b>5.35</b>	 <b>5.39</b>	95
2	 <b>5.36</b>	 <b>5.40</b>	52 <sup>b</sup>
3	 <b>5.37</b>	 <b>5.41</b>	70 <sup>c</sup>
4	 <b>5.38</b>	 <b>5.42</b>	93 <sup>c,d</sup>

<sup>a</sup> Yields of purified products. <sup>b</sup> 10 mol % catalyst. <sup>c</sup> 2:1 *E*:*Z* determined by <sup>1</sup>H NMR analysis. <sup>d</sup> 10 mol % catalyst with PPh<sub>3</sub> as the ligand.

Due to the likely isomerization of the Ni- $\pi$ -allyl complex during the borylation reaction, terminal boronates bearing *E*-olefins are normally formed with excellent selectivity, as demonstrated in Tables 5.3 and 5.4. Remarkably, when 1,1,2-trisubstituted allylic acetates (e.g. *E*-**5.43** and *Z*-**5.43** in Scheme 5.7) are used as substrates for this transformation, the olefin geometry remains completely untouched, likely due to the much slower isomerization with increased substitution. As shown in Scheme 7, both *E* and *Z* allylic boronates were synthesized in magnificent yields and in exceedingly high isomeric purity from the corresponding allylic acetates, respectively.

### Scheme 5.7



**C. The Pd-Catalyzed Allylic Borylation.** Preliminary studies on Pd-catalyzed allylic borylation, as discussed earlier in this chapter, led to promising reaction conditions wherein base additives (e.g.  $\text{Cs}_2\text{CO}_3$ ) are employed to increase substrate conversion from less than 5% to up to 90% (entry 5, Table 5.1), presumably through activating  $\text{B}_2(\text{pin})_2$  in the transmetallation step. We anticipated that  $\pi$ -allylmetal complexes derived from allylic halides might be more reactive than those derived from allylic acetates since ligand exchange with halides might be more facile. The initial exploration of allylhalides as substrate is given in Table 5.5. To our delight, cinnamyl bromide was fully converted to cinnamyl $\text{B}(\text{pin})$  under the catalysis of  $\text{Pd}_2(\text{dba})_3$  in THF, with only 1 equivalent of diboron reagent (entry 2). The isolated product, however, was contaminated by an unknown impurity, which could not be removed by silica gel chromatography nor avoided by manipulating the reaction conditions (entries 3 and 4). Replacing the bromide with chloride affords a slower yet cleaner reaction (entry 5). During the reaction, we noticed that significant amount of palladium black precipitates on the side and bottom of

the reaction vessels. The appearance of palladium black is likely the origin of low the conversions observed. Therefore, catalyst concentration was reduced. This proved beneficial (entries 7 and 8); with a quarter of the original catalyst loading, the borylation delivers 68% yield of pure cinnamylB(pin) out of a full conversion reaction. Further lowering the amount of Pd<sub>2</sub>(dba)<sub>3</sub> and increasing concentration of starting materials, the reaction is superior, yielding pure product in 90% yield (entry 9).

**Table 5.5 Condition Optimization for Pd-Catalyzed Allylic Borylation**

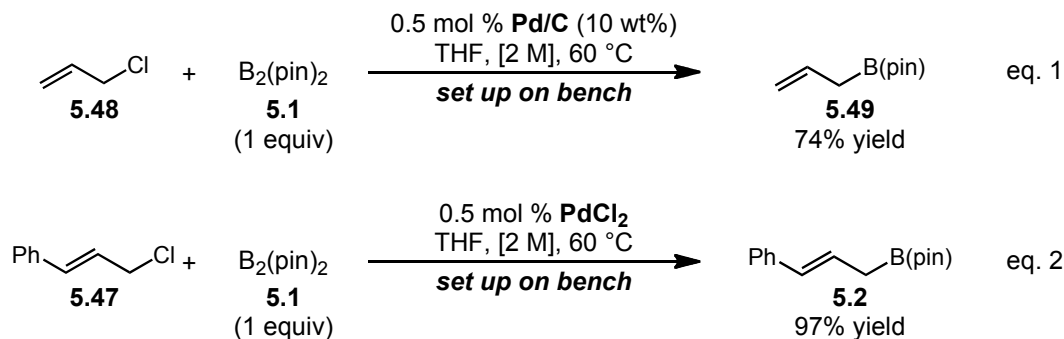
entr y		catalyst	conc.	temp.	time	%conv. <sup>a</sup> (%yield <sup>b</sup> )
1		10 mol % Ni(cod) <sub>2</sub> /PPh <sub>3</sub>	0.5 M	60 °C	12 h	<5
2	 5.46	5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	12 h	100 (66 <sup>c</sup> )
3		5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	rt	12 h	100 (69 <sup>c</sup> )
4		2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	12 h	100 (85 <sup>c</sup> )
5		5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	12 h	85
6		5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	18 h	86
7	 5.47	2.5 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	12 h	90
8		1.25 mol % Pd <sub>2</sub> (dba) <sub>3</sub>	0.5 M	60 °C	12 h	100 (68)
<b>9</b>		<b>0.25 mol % Pd<sub>2</sub>(dba)<sub>3</sub></b>	<b>2 M</b>	<b>60 °C</b>	<b>12 h</b>	<b>100 (90)</b>

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR analysis. <sup>b</sup> Yields of purified products. <sup>c</sup> Isolated products were not clean, containing ~10% unknown impurity.

It is worth noting that the Pd-catalyzed carbon-boron coupling between allylic halides and B<sub>2</sub>(pin)<sub>2</sub> is more than just an alternative for the Ni-catalysis procedure; it presents a highly efficient and extremely practical method for the synthesis of allylic

boronate reagents, in which: (1) the catalysts are exceedingly active with very high turnover, so that only 0.5 mol % of catalyst is needed to complete the transformation, (2) as shown in scheme 5.8, multiple air stable and commercially available Pd(II) sources (e.g. PdCl<sub>2</sub>, Pd/C) can be employed as catalysts as well, which allows the borylation to be set up on the bench-top, without the assistance of a dry box. The high concentration, low catalyst loading and air-stable procedure allow for potential large-scale applications in industrial processes. Additionally, since Pd is used more often in the carbon-carbon or carbon-hetero atom cross-coupling reactions than Ni, this method is very promising for the future development of one-pot borylation/cross-coupling sequences.

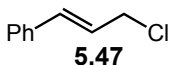
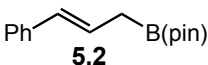
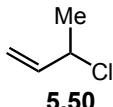
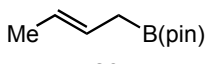
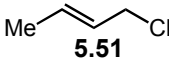
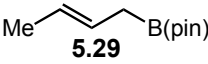
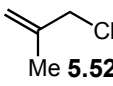
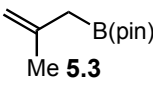
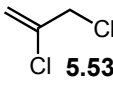
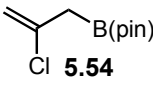
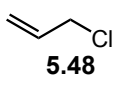
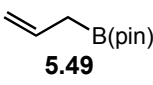
**Scheme 5.8**



The representative substrate scope is given in Table 5.6. Allylchlorides bearing various substituents can be smoothly converted to the corresponding terminal allylic boronates with high levels of *E*-selectivity. The only exception is crotylB(pin), wherein only 76% *E*-isomer is presented. β-Chloro-allylB(pin) (**5.54**) was synthesized from the commercially available dichloride (**5.53**). Note that the vinyl chloride functionality stays untouched during the borylation.

**Table 5.6 Substrate Scope in the Pd-Catalyzed Allylic Borylation**

$$\text{R}-\text{CH}=\text{CH}-\text{CH}_2\text{Cl} \xrightarrow[\text{1.0 equiv B}_2(\text{pin})_2]{\text{0.5 mol \% "Pd", THF, [2 M], 60 }^\circ\text{C}} \text{R}-\text{CH}=\text{CH}-\text{CH}_2\text{B}(\text{pin})$$

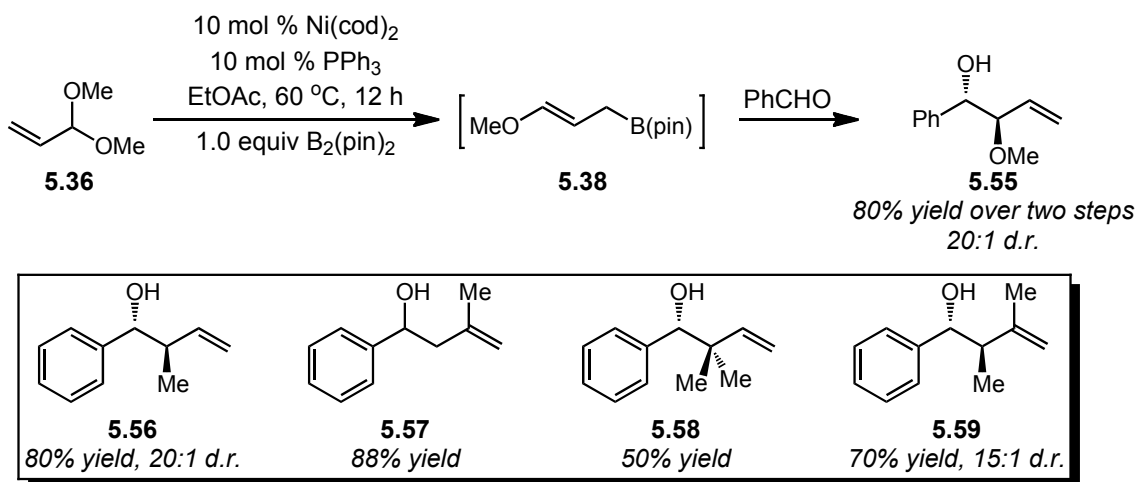
entry	sustrate	product	<i>Pd</i> <sub>2</sub> ( <i>dba</i> ) <sub>3</sub> %yield <sup>a</sup>	<i>PdCl</i> <sub>2</sub> , on bench %yield <sup>a</sup>
1	 <b>5.47</b>	 <b>5.2</b>	90	97
2	 <b>5.50</b>	 <b>5.29</b>	77 <sup>b</sup>	81 <sup>b</sup>
3	 <b>5.51</b>	 <b>5.29</b>	70 <sup>b</sup>	70 <sup>b</sup>
4	 <b>5.52</b>	 <b>5.3</b>	67	70 <sup>c</sup>
5	 <b>5.53</b>	 <b>5.54</b>	69 <sup>c</sup>	69 <sup>c</sup>
6	 <b>5.48</b>	 <b>5.49</b>	79	80

<sup>a</sup> Yields of purified products. <sup>b</sup> 6:1 *E:Z*. <sup>c</sup> 1 Equiv of KOAc was used.

**D. One-Pot Allylic Borylation/Allylboration.** With ready access to a variety of functionalized and substituted allylboron reagents, important synthetic motifs can be easily prepared from widely available allylic acetates and allylic halides. As one example, benzaldehyde was directly added into the unquenched Ni-catalyzed borylation mixture. This furnished allylation products in a highly diastereoselective fashion in great yields (Scheme 5.9). In general, the isolation of allylic boronates is simple, because the borylation reactions are clean and the products stable on silica gel for a short period of

time. However there are a couple of exceptions, such as crotylB(pin) (Table 5.3, entry 2), which is accompanied with ~10% byproduct derived from the hydroboration of 1,5-cyclooctadiene, and  $\gamma$ -oxygenated allylB(pin) (**5.38**), which slowly decomposes during chromatographic purification. Importantly with the one-pot borylation/allylboration sequence, the homoallylic alcohols were obtained as single compounds in excellent yields and with high level of diastereocontrol.

#### Scheme 5.9



## IV. CONCLUSION

In summary, inspired by the Miyaura reaction we have developed Ni- and Pd-catalyzed allylic borylations. . Starting with readily available and easily accessed allylic acetates and allylic halides, highly functionalized and substituted allylborates can be achieved in high yields with excellent stereocontrol. Both reactions employ commercially available metal sources and are highly efficient, presenting ideal methods for the preparation of synthetically useful allylboron building blocks. The Pd-catalyzed carbon-

boron coupling, in particular, features low catalyst loading, high concentration as well as air- and moisture-stable set-up procedure, allowing future applications in large-scale syntheses in industrial processes. The direct allylboration of aldehydes through the use of the crude reaction mixtures have also been demonstrated, furnishing the corresponding alcohols in high yields and with extraordinary diastereocontrol.

## V. EXPERIMENTAL PROCEDURES

### A. General Information

$^1\text{H}$  NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz) or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the reference ( $\text{CDCl}_3$ : 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and assignment.  $^{13}\text{C}$  NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Gemini-500 (125 MHz) or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the reference ( $\text{CDCl}_3$ : 77.0 ppm). Carbons with directly attached boron atoms were not observed in some compounds, most likely due to quadrupolar relaxation.<sup>20</sup> Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer,  $\nu_{\text{max}}$   $\text{cm}^{-1}$ . Bands are characterized as broad (br), strong (s), medium (m), and weak (w).

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<sup>20</sup> Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, 12, 227.

High-resolution mass spectra (ESI) were obtained at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed through the use of forced flow (flash chromatography) on silica gel ( $\text{SiO}_2$ , 230 $\times$ 450 mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25  $\mu\text{m}$  silica gel plates purchased from Silicycle. Visualization was performed through the use of ultraviolet light (254 nm) or potassium permanganate ( $\text{KMnO}_4$ ) in water.

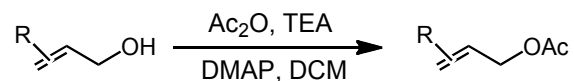
All reactions were conducted in oven- or flame-dried glasswares under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) was purified through the use of a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Ethyl acetate was purified by drying with calcium hydride and distilled under  $\text{N}_2$ . Dimethyl sulfoxide (DMSO) was purified by drying with calcium hydride and distilled under high vacuum. Benzaldehyde was freshly distilled under high vacuum right prior to use. Tricyclohexylphosphine ( $\text{PCy}_3$ ), tris(dibenzylideneacetone) dipalladium(0) [ $\text{Pd}_2(\text{dba})_3$ ], bis(1,5-cyclooctadiene)nickel(0) [ $\text{Ni}(\text{cod})_2$ ] were purchased from Strem Chemicals, Inc. 2-Methylallyl acetate was purchased from Tokyo Chemical Industry (TCI). Bis(pinacolato)diboron [ $\text{B}_2(\text{pin})_2$ ] was obtained from Allylchem Co., Ltd. and recrystallized from pentane prior to use. All other reagents were purchased from either Fisher or Aldrich and used without further purification.



## B. Experimental Procedures

### 1. Preparation and Characterization of Allylic Acetates

**Representative Procedure for the Synthesis of Allylic Acetates.** The allylic acetate substrates, if not commercially available, were generally prepared through the acetylation of corresponding allylic alcohols.



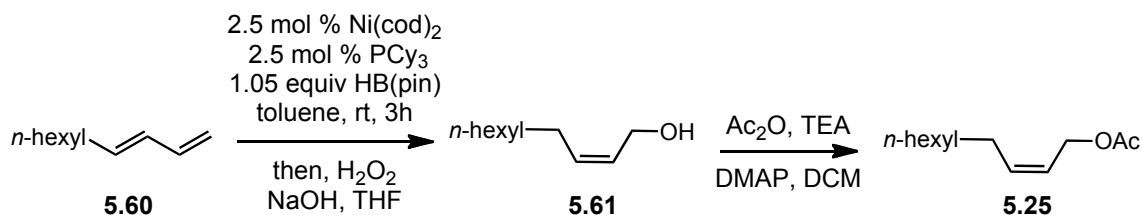
The following allylic acetates were prepared from commercially available allylic alcohols: hex-1-en-3-yl acetate (**5.23**),<sup>21</sup> (E)-3-(benzo[d][1,3]dioxol-5-yl)allyl acetate(**5.35**)<sup>22</sup> and (E)-2-methylbut-2-en-1-yl acetate (**5.27**).<sup>23</sup> Spectral data are in accordance with the literature references.

<sup>21</sup> Strazzolini, P.; Giumanin, A. G.; Verardo, G. *Tetrahedron* **1994**, 50, 217.

<sup>22</sup> Kumar, V.; Sharma, A.; Sharma, M. Sharma, U. K.; Shiha, A. K. *Tetrahedron* **2007**, 63, 9718.

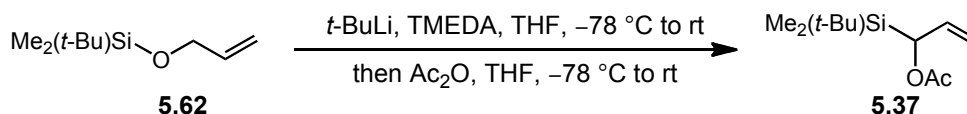
<sup>23</sup> Rowan, D. D.; Heather, P.; Allen, J. M.; Fielder, S.; Hunt, M. B. *J. Agric. Food. Chem.* **1996**, 44, 3276.

**Preparation of (Z)-dec-2-en-1-yl acetate (5.25).** From allylic alcohol **5.61**, which was synthesized through Ni-catalyzed hydroboration of decadiene as shown below.<sup>8c</sup>



*n*-hexyl—CH=CH—CH<sub>2</sub>—OAc (**(Z)-dec-2-en-1-yl acetate (5.25)**). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 0.88 (3H, t, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.27-1.39 (10H, m, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 2.06 (3H, s, COCH<sub>3</sub>), 2.09 (2H, q, *J* = 7.4 Hz, CH<sub>2</sub>CH<sub>2</sub>CH=CH), 4.61 (2H, dd, *J* = 6.3, 0.6 Hz, CH=CHCH<sub>2</sub>O), 5.49-5.55 (1H, m, CH<sub>a</sub>=CH<sub>b</sub>), 5.62-5.67 (1H, m, CH<sub>a</sub>=CH<sub>b</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 14.1, 21.0, 22.6, 27.5, 29.12, 29.14, 29.4, 31.8, 60.4, 123.2, 135.5, 171.0; IR (neat): 2956.4 (w), 2924.9 (m), 2855.2 (w), 1740.0 (s), 1459.1 (w), 1371.5 (m), 1225.0 (s), 1024.6 (m), 962.8 (w), 840.5 (w), 643.4 (w), 606.8 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>12</sub>H<sub>26</sub>NO<sub>2</sub> [M+NH<sub>4</sub>]: calculated: 216.1964, found: 216.1969. The unpurified reaction mixture was purified on silica gel (flushed with 100:1 hexanes/EtOAc) to afford 2.13 g (95% yield) of (Z)-dec-2-en-1-yl acetate as a colorless oil. R<sub>f</sub> = 0.53 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).

**Preparation of 1-(tert-butyldimethylsilyl)allyl acetate (5.37).** From commercially available (allyloxy)(tert-butyl)dimethylsilane (**5.62**), procedure was modified from literature.<sup>24</sup>

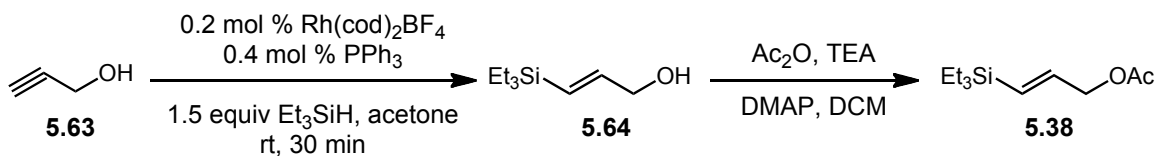


**1-(tert-butyldimethylsilyl)allyl acetate (5.37).** To a flame-dried round-bottom flask equipped with a stir bar was added (allyloxy)(tert-butyl)dimethylsilane (345 mg, 2.0 mmol), tetramethylethylenediamine (TMEDA, 326 mg, 2.8 mmol) and THF (4 mL). The reaction was cooled to  $-78\text{ }^\circ\text{C}$  and 1.6 M *tert*-butyllithium in pentane (1.5 mL, 2.4 mmol) was added dropwise over 10 minutes, *via* syringe. The reaction was allowed to slowly warm up to room temperature. After stirring for another 30 minutes, the reaction was cooled to  $-78\text{ }^\circ\text{C}$  and quenched with acetic anhydride (283 mg, 2.8 mmol) in THF (0.25 mL). The reaction was allowed to warm to room temperature and to stir for another hour. Then water was added slowly, and the reaction was extracted into diethyl ether three times. The combined organic layers were washed with saturated  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (50:1 hexanes/ $\text{Et}_2\text{O}$ ) to afford 162 mg (38% yield) of 1-(tert-butyldimethylsilyl)allyl acetate as

<sup>24</sup> Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 9153.

colorless oil.  $R_f = 0.52$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ). Spectral data are in accordance with the literature references.<sup>25</sup>

**Preparation of (*E*)-3-(triethylsilyl)allyl acetate (5.38).** From (*E*)-3-(triethylsilyl)prop-2-en-1-ol (**5.64**), which was synthesized through the Rh-catalyzed hydrosilylation of prop-2-yn-1-ol as shown below.<sup>26</sup>



**(*E*)-3-(triethylsilyl)allyl acetate (5.38).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.58 (6H, q,  $J = 8.1$  Hz,  $\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 0.93 (9H, t,  $J = 8.1$  Hz,  $\text{Si}(\text{CH}_2\text{CH}_3)_3$ ), 2.10 (3H, s,  $\text{COCH}_3$ ), 4.60 (2H, dd,  $J = 5.1, 1.5$  Hz,  $\text{CH}=\text{CHCH}_2\text{OAc}$ ), 5.87 (1H, dt,  $J = 19.0, 1.5$  Hz,  $\text{CH}=\text{CHCH}_2\text{OAc}$ ), 6.07 (1H, dt,  $J = 18.9, 5.1$  Hz,  $\text{CH}=\text{CHCH}_2\text{OAc}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.3, 7.3, 21.0, 67.1, 129.8, 140.5, 170.7; IR (neat): 2953.2 (w), 2910.9 (w), 2875.3 (w), 1743.3 (s), 1623.7 (w), 1458.1 (w), 1416.2 (w), 1376.2 (w), 1226.6 (s), 1068.7 (w), 1014.8 (m), 985.9 (m), 845.2 (w), 777.7 (m), 760.1 (m), 718.0 (s), 637.1 (w), 606.2 (w); HRMS (ESI+) for  $\text{C}_{11}\text{H}_{23}\text{O}_2\text{Si}$  [ $\text{M}+\text{H}$ ]: calculated: 215.1467, found: 215.1463. The unpurified reaction mixture was purified on silica gel (flushed with 30:1 hexanes/EtOAc) to afford 1.21 g (90% yield) of (*E*)-3-(triethylsilyl)allyl acetate as a colorless oil.  $R_f = 0.54$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).

<sup>25</sup> Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873.

<sup>26</sup> Takeuchi, R.; Nitta, S.; Watanabe, D. *J. Org. Chem.* **1995**, *60*, 3045.

**2. Representative Procedure for Pd<sub>2</sub>(dba)<sub>3</sub>-Catalyzed Allylic Borylation (Table 5.5 and Table 5.6).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (2.3 mg, 0.0025 mmol), bis(pinacolato)diboron (254 mg, 1.0 mmol), THF (0.5 mL) and cinnamylchloride (153 mg, 1.0 mmol), sequentially, in a dry-box under an argon atmosphere. The vial was capped and sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. The vial was then cooled to ambient temperature, and the reaction mixture was directly analyzed through the use of <sup>1</sup>H NMR to determine the conversion of reaction. Silica gel chromatography (50:1 pentane/Et<sub>2</sub>O) afforded 220 mg (90% yield) of 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as colorless oil.

**3. Representative Procedures for Pd<sub>2</sub>(dba)<sub>3</sub>-Catalyzed Allylic Borylation with Base (Table 5.1).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (22.9 mg, 0.025 mmol), bis(pinacolato)diboron (127 mg, 0.5 mmol), THF (1 mL), 2-methylallyl acetate (57.1 mg, 0.5 mmol) and cesium carbonate (489 mg, 1.5 mmol) sequentially, in a dry-box under an argon atmosphere. The vial was capped and sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. The vial was then cooled to ambient temperature. The reaction was diluted with diethyl ether, filtered through a plug of silica gel, washed with more diethyl ether, and concentrated in *vacuo*. Analysis of unpurified reaction mixture through the use of <sup>1</sup>H NMR was used to determine the conversion of reaction. The conversion of 2-methylallyl acetate was 84% and no purification was conducted.

**4. Representative Procedure for PdCl<sub>2</sub>-Catalyzed Allylic Borylation (Table 5.6 and Table 5.8).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with palladium(II) chloride (0.9 mg, 0.005 mmol) and bis(pinacolato)diboron (254 mg, 1.0 mmol) in a dry-box under an argon atmosphere. The vial was sealed with a septum, removed from the dry-box, and THF (0.5 mL) was added by syringe under N<sub>2</sub> atmosphere, followed by cinnamylchloride (153 mg, 1.0 mmol). The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature, and the reaction mixture was directly analyzed through the use of <sup>1</sup>H NMR to determine the conversion of reaction. Silica gel chromatography (50:1 pentane/Et<sub>2</sub>O) afforded 237 mg (97% yield) of 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as colorless oil.

**5. Representative Procedure for PdCl<sub>2</sub>-Catalyzed Allylic Borylation with Additive (Table 5.6).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with palladium(II) chloride (0.9 mg, 0.005 mmol), bis(pinacolato)diboron (254 mg, 1.0 mmol) and potassium acetate (98.2 mg, 1.0 mmol) in a dry-box under an argon atmosphere. The vial was sealed with a septum, removed from the dry-box, and THF (0.5 mL) was added by syringe under N<sub>2</sub> atmosphere, followed by 2-methylallyl chloride (90.1 mg, 1.0 mmol). The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature. The reaction was diluted with diethyl ether, filtered through a plug of silica gel, washed with more diethyl ether, and concentrated in *vacuo*. Analysis of

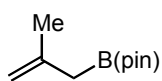
unpurified reaction mixture through the use of  $^1\text{H}$  NMR was used to determine the conversion of reaction. Silica gel chromatography (50:1 pentane/ $\text{Et}_2\text{O}$ ) afforded 127 mg (70% yield) of (*E*)-2-(but-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as colorless oil.

**6. Representative Procedures for  $\text{Ni}(\text{cod})_2$ -Catalyzed Allylic Borylation (Table 5.2, Table 5.3 and Table 5.4).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with bis(1,5-cyclooctadiene)nickel(0) (6.9 mg, 0.025 mmol), tricyclohexylphosphine (7.0 mg, 0.025 mmol) and  $\text{EtOAc}$  (1.0 mL) in a dry-box under an argon atmosphere. Cinnamyl acetate (88.1 mg, 0.5 mmol) was then added, followed by bis(pinacolato)diboron (127 mg, 0.5 mmol). The vial was capped and sealed, removed from the dry-box, and allowed to stir at 60  $^\circ\text{C}$  for 12 hours. The vial was then cooled to ambient temperature, and the reaction mixture was directly analyzed through the use of  $^1\text{H}$  NMR to determine the conversion of reaction. Silica gel chromatography (50:1 pentane/ $\text{Et}_2\text{O}$ ) afforded 224 mg (92% yield) of 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as colorless oil.

## 7. Characterization and Proof of Stereochemistry

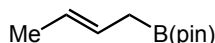
 **2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.2).** The

unpurified reaction mixture was purified on silica gel (50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (109.9 mg, 90% yield).  $R_f$  = 0.45 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). Spectral data are in accordance with the literature references.<sup>27</sup>



**4,4,5,5-tetramethyl-2-(2-methylallyl)-1,3,2-dioxaborolane (5.3).** The

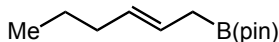
unpurified reaction mixture was purified on silica gel (50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (60.0 mg, 67% yield).  $R_f$  = 0.49 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). Spectral data are in accordance with the literature references.<sup>10, 28</sup>



**(E)-2-(but-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

**(5.29).** The unpurified reaction mixture was purified on silica gel

(50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (76.5 mg, 84% yield) with 5% (Z)-2-(cyclooct-4-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as impurity from <sup>1</sup>H NMR analysis.  $R_f$  = 0.55 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). Spectral data are in accordance with the literature references.<sup>29</sup>



**(E)-2-(hex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

**(5.30).** Spectral data are in accordance with the literature references.<sup>12b</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.86 (3H, t,  $J$  = 9 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.21 (12 H, s, (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.29-1.39 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.62 (2H, d,  $J$  = 8.0 Hz, CH<sub>2</sub>B), 1.95 (2H, app q,  $J$  = 8.5 Hz,

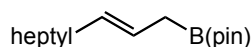
<sup>27</sup> Selander, N.; Szabó, K. J. *J. Org. Lett.* **2009**, 74, 5695.

<sup>28</sup> Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, 132, 10686.

<sup>29</sup> Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, 108, 3422.

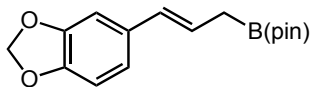


CH<sub>2</sub>CH<sub>2</sub>CH=CH), 5.33-5.47 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CH=CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 13.6, 22.7, 24.7, 34.8, 83.1, 124.8, 130.8; IR (neat): 2978.1 (w), 2959.3 (w), 2929.4 (w), 2872.7 (w), 1457.7 (w), 1359.0 (m), 1323.3 (s), 1142.9 (s), 965.8 (s), 846.8 (m), 673.8 (m), 520.0 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>12</sub>H<sub>24</sub>BO<sub>2</sub> [M+H]: calculated: 211.1869, found: 211.1876. The unpurified reaction mixture was purified on silica gel (50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (99.3 mg, 94% yield). R<sub>f</sub> = 0.6 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).



**(*E*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

**(5.31).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 0.87 (3H, t, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.20-1.37 (22 H, m, CH<sub>3</sub>(CH<sub>2</sub>)<sub>5</sub> and (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.63 (2H, d, *J* = 6.0 Hz, CH<sub>2</sub>B), 1.96 (2H, app q, *J* = 6.5 Hz, CH<sub>2</sub>CH<sub>2</sub>CH=CH), 5.31-5.46 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CH=CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 14.1, 22.7, 24.7, 29.1, 29.2, 29.7, 31.9, 32.7, 83.1, 124.6, 131.1 ppm; IR (neat): 2976.1 (w), 2956.3 (w), 2928.4 (w), 1460.7 (w), 1356.3 (m), 1321.2 (s), 1141.0 (s), 962.3 (s), 842.3 (m), 671.1 (m), 654.2 (m), 431.2 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>16</sub>H<sub>32</sub>BO<sub>2</sub> [M+H]: calculated: 267.2469, found: 267.2472. The unpurified reaction mixture was purified on silica gel (50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (122.5 mg, 92% yield). R<sub>f</sub> = 0.66 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).

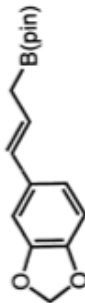


**(*E*)-2-(3-(benzo[*d*][1,3]dioxol-5-yl)allyl)-4,4,5,5-tetramethyl-**

**1,3,2-dioxaborolane (5.39).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):

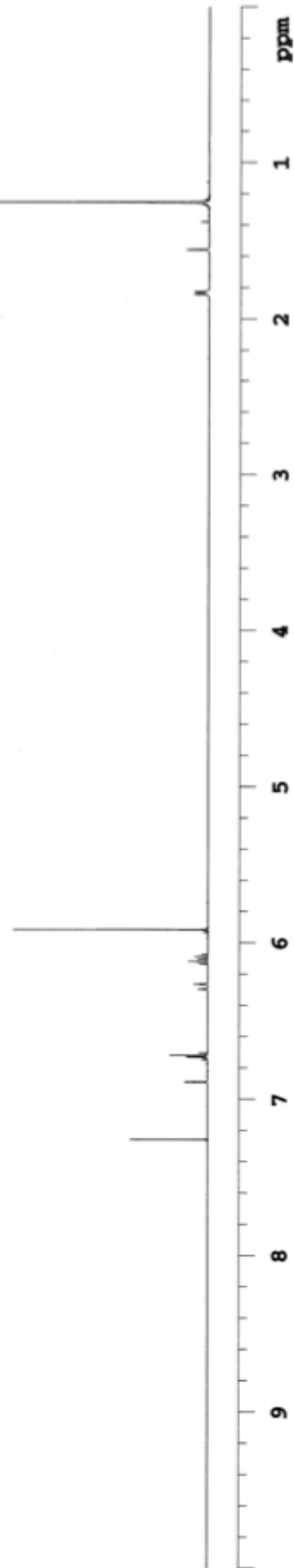
δ 1.26 (12H, s, (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.84 (2H, d, *J* = 7.3 Hz, CH=CHCH<sub>2</sub>B), 5.93 (2H, s,

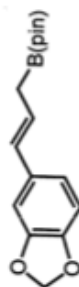
OCH<sub>2</sub>O), 6.10 (1H, dt,  $J = 15.6, 7.6$  Hz, CH=CHCH<sub>2</sub>B), 6.28 (1H, d,  $J = 15.6$  Hz, CH=CHCH<sub>2</sub>B), 6.70-6.75 (2H, m, ArH), 6.89 (1H, s, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  24.8, 83.4, 100.8, 105.4, 108.1, 120.0, 124.9, 129.8, 132.8, 146.3, 147.8; IR (neat): 2977.6 (w), 2930.4 (w), 2877.4 (w), 1488.8 (m), 1442.3 (m), 1360.4 (m), 1326.8 (s), 1276.2 (s), 1248.0 (s), 1140.5 (s), 1119.6 (s), 1033.3 (s), 963.3 (s), 929.1 (s), 876.8 (s), 844.9 (m), 799.8 (s), 521.2 (m) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>16</sub>H<sub>22</sub>BO<sub>4</sub> [M+H]: calculated: 289.1611, found: 289.1612. The unpurified reaction mixture was purified on silica gel (10:1 pentane/Et<sub>2</sub>O) to afford a white solid (108.4 mg, 95% yield).  $R_f = 0.33$  (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). Melting point: 48 °C.



Temp. 25.0 C / 298.1 K  
Operator: roundtri  
INOVA-500 "nmr16"

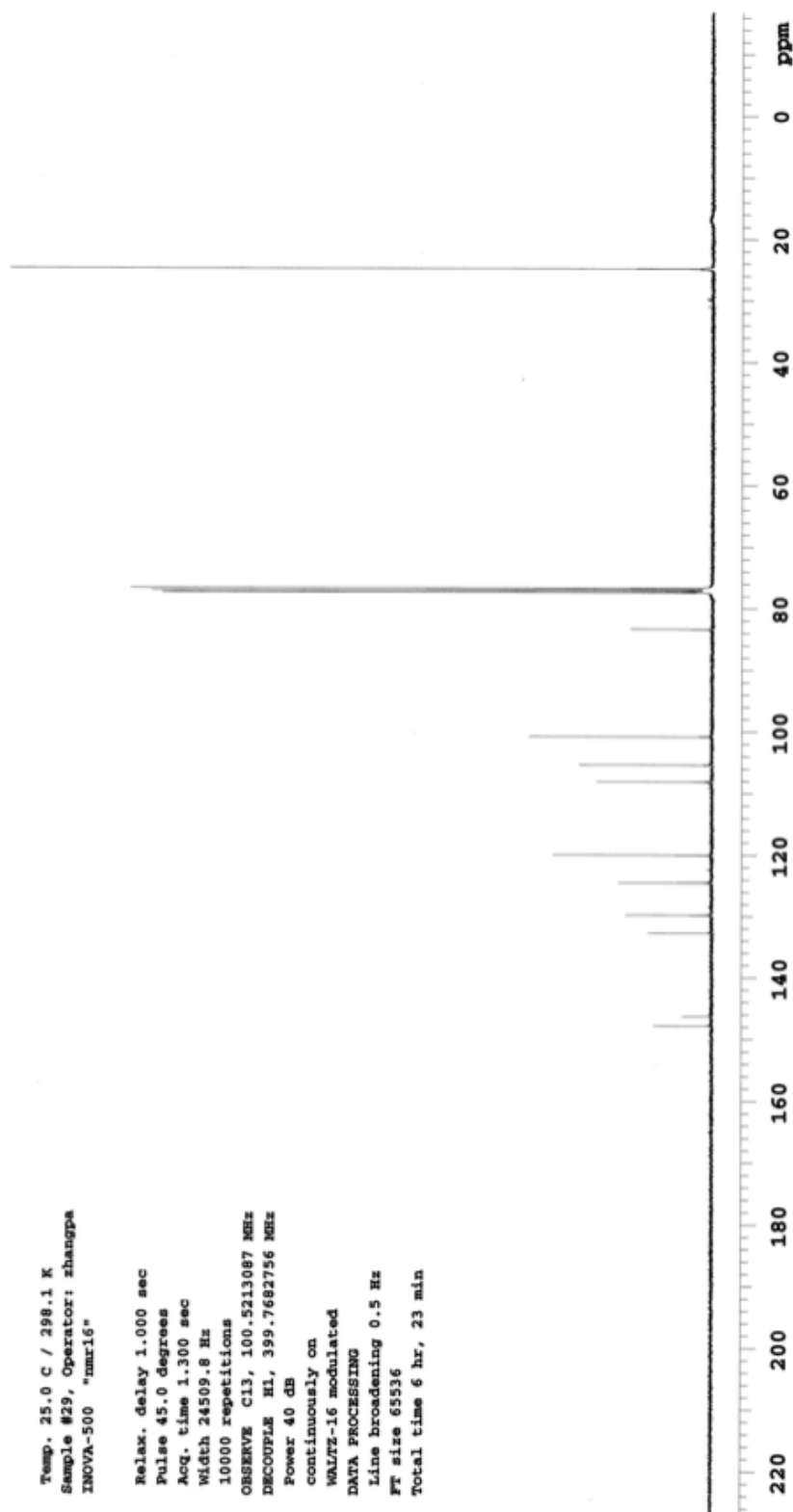
Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 2.049 sec  
Width 8012.8 Hz  
16 repetitions  
OBSERVE H1, 499.8808006 MHz  
DATA PROCESSING  
Resol. enhancement -0.0 Hz  
Ft size 65536  
Total time 0 min 55 sec

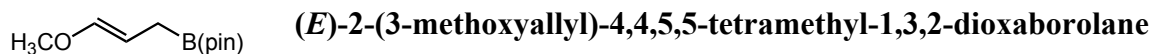




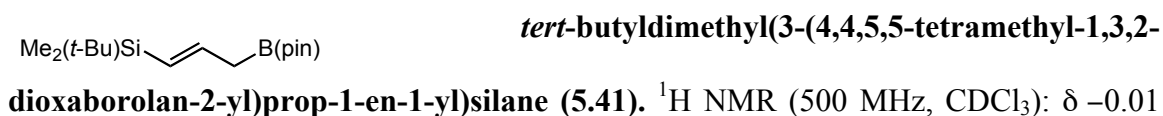
Temp. 25.0 C / 298.1 K  
 Sample #29, Operator: zhangpa  
 INOVA-500 "nmr16"

Relax. delay 1.000 sec  
 Pulse 45.0 degrees  
 Acq. time 1.300 sec  
 Width 24509.8 Hz  
 10000 repetitions  
 OBSERVE C13, 100.5213087 MHz  
 DECOUPLE H1, 399.7682756 MHz  
 Power 40 dB  
 continuously on  
 WALTZ-16 modulated  
 DATA PROCESSING  
 Line broadening 0.5 Hz  
 FT size 65536  
 Total time 6 hr, 23 min



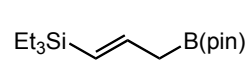


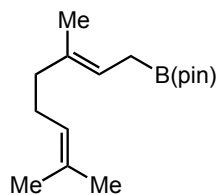
**(5.40).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.26 (12H, s, (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.51 (2H, d, *J* = 7.4 Hz, CH=CHCH<sub>2</sub>B), 3.49 (3H, s, OCH<sub>3</sub>), 4.76 (1H, dt, *J* = 12.7, 7.3 Hz, CH=CHCH<sub>2</sub>B), 6.27 (1H, d, *J* = 12.7 Hz, CH=CHCH<sub>2</sub>B); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 24.8, 55.9, 83.2, 97.8, 147.0; IR (neat): 2978.5 (w), 2934.0 (w), 1653.3 (w), 1358.5 (m), 1321.9 (s), 1272.5 (w), 1212.0 (m), 1143.5 (s), 1123.0 (s), 1105.6 (m), 967.2 (m), 881.2 (m), 845.7 (m), 673.2 (w), 539.8 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>10</sub>H<sub>20</sub>BO<sub>3</sub> [M+H]: calculated: 199.1506, found: 199.1497. The unpurified reaction mixture was purified on silica gel (100:1 → 25:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (51.5 mg, 52% yield). *R*<sub>f</sub> = 0.38 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ -0.01 (*E*, 6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), 0.09 (*Z*, 6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), 0.85 (*E*, 9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.88 (*Z*, 9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.236 (*E*, 12H, s, (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.243 (*Z*, 12H, s, (C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.82-1.85 (2H, m, CH=CHCH<sub>2</sub>B), 5.47 (*Z*, 1H, dt, *J* = 14.2, 1.3 Hz, CH=CHCH<sub>2</sub>B), 5.60 (*E*, 1H, dt, *J* = 18.5, 1.5 Hz, CH=CHCH<sub>2</sub>B), 6.08 (*E*, 1H, dt, *J* = 18.5, 7.2 Hz, CH=CHCH<sub>2</sub>B), 6.51 (*Z*, 1H, dt, *J* = 14.2, 8.3 Hz, CH=CHCH<sub>2</sub>B); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ -6.1, -4.1, 10.6, 16.5, 24.6, 24.71, 24.74, 26.4, 26.5, 30.9, 83.2, 82.3, 125.2, 127.5, 143.4, 144.7; IR (neat): 2978.7 (w), 2952.5 (w), 2927.7 (w), 2884.2 (w), 2855.3 (w), 2040.0 (w), 1744.4 (w), 1608.6 (w), 1470.0 (w), 1370.5 (w), 1323.6 (s), 1272.0 (w), 1247.2 (m), 1214.7 (w), 1164.7 (w), 1143.7 (s), 1105.0 (w), 1006.7 (w), 986.9 (w), 967.0 (w), 938.0

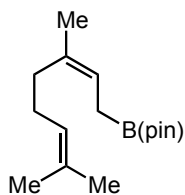
(w), 885.2 (w), 847.9 (w), 825.5 (s), 810.0 (m), 773.8 (m), 715.8 (w), 576.9 (w), 545.7 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{32}\text{BO}_2\text{Si}$   $[\text{M}+\text{H}]$ : calculated: 283.2265, found: 283.2257. The unpurified reaction mixture was purified on silica gel (pentane  $\rightarrow$  100:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (98.7 mg, 70% yield) as a mixture of *E* and *Z* isomers (2.5:1 *E*:*Z*).  $R_f$  = 0.61 (8:1 hexanes/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ ).


**triethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)silane (5.42).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.53 (*E*, 6H, q,  $J$  = 8.0 Hz,  $(\text{CH}_3\text{CH}_2)_3\text{Si}$ ), 0.62 (*Z*, 6H, q,  $J$  = 8.0 Hz,  $(\text{CH}_3\text{CH}_2)_3\text{Si}$ ), 0.88-0.96 (9H, m,  $(\text{CH}_3\text{CH}_2)_3\text{Si}$ ), 1.24 (*E*, 12H, s,  $(\text{C}(\text{CH}_3)_2)_2$ ), 1.26 (*Z*, 12H, s,  $(\text{C}(\text{CH}_3)_2)_2$ ), 1.83 (2H, d,  $J$  = 7.5 Hz,  $\text{CH}=\text{CHCH}_2\text{B}$ ), 5.38 (*Z*, d,  $J$  = 14.0 Hz,  $\text{SiCH}=\text{CHCH}_2$ ), 5.53 (*E*, d,  $J$  = 18.5 Hz,  $\text{SiCH}=\text{CHCH}_2$ ), 6.08 (*E*, dt,  $J$  = 18.5, 7.5 Hz,  $\text{SiCH}=\text{CHCH}_2$ ), 6.08 (*Z*, dt,  $J$  = 14.0, 7.5 Hz,  $\text{SiCH}=\text{CHCH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.6, 4.6, 7.3, 7.5, 24.8, 83.2, 124.6, 126.3, 143.5, 145.0; IR (neat): 2978.8 (w), 2952.2 (w), 2910.4 (w), 2874.3 (w), 1609.1 (w), 1323.0 (s), 1143.5 (s), 1013.9 (w), 987.1 (w), 966.7 (w), 847.8 (w), 716.0 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{15}\text{H}_{32}\text{BO}_2\text{Si}$   $[\text{M}+\text{H}]$ : calculated: 283.2265, found: 283.2258. The unpurified reaction mixture was purified on silica gel (pentane  $\rightarrow$  100:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (131.2 mg, 93% yield) as a mixture of *E* and *Z* isomers (2.2:1 *E*:*Z*).  $R_f$  = 0.60 (8:1 hexanes/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ ).



**(E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (E-5.44).** The unpurified reaction mixture was purified

on silica gel (50:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (131.9 mg, quat. yield).  $R_f$  = 0.55 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). Spectral data are in accordance with the literature references.<sup>8b, 13</sup>

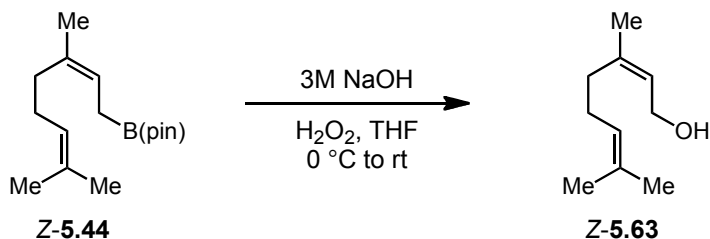


**(Z)-2-(3,7-dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Z-5.44).** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.24 (12H, s,

(C(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 1.61 (5H, m, (CH<sub>3</sub>)<sub>a</sub>C=CH and CH<sub>2</sub>B), 1.68 (3H, s, (CH<sub>3</sub>)<sub>b</sub>C=CH), 1.69 (3H, s, (CH<sub>3</sub>)<sub>c</sub>C=CH), 2.00-2.06 (4H, m, CCH<sub>2</sub>CH<sub>2</sub>C), 5.13 (1H, tq,  $J$  = 7.0, 1.5 Hz, (C=CH)<sub>a</sub>CH<sub>2</sub>), 5.24 (1H, tq,  $J$  = 7.5, 1.5 Hz, (C=CH)<sub>b</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):

δ 17.6, 23.5, 24.8, 25.7, 26.4, 31.8, 83.1, 119.1, 124.5, 131.3, 135.2; IR (neat): 2976.9 (w), 2925.8 (w), 2856.7 (w), 1448.1 (w), 1370.6 (w), 1340.6 (s), 1322.2 (s), 1272.6 (w), 1214.3 (w), 1143.2 (s), 1106.4 (w), 1074.8 (w), 967.4 (m), 884.5 (m), 845.2 (m), 674.5 (w) 577.8 (w) cm<sup>-1</sup>; HRMS (ESI+) for C<sub>16</sub>H<sub>30</sub>BO<sub>2</sub> [M+H]: calculated: 265.2339, found: 265.2350. The unpurified reaction mixture was purified on silica gel (pentane → 100:1 pentane/Et<sub>2</sub>O) to afford a clear, colorless oil (131.5 mg, quat. yield).  $R_f$  = 0.55 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>).

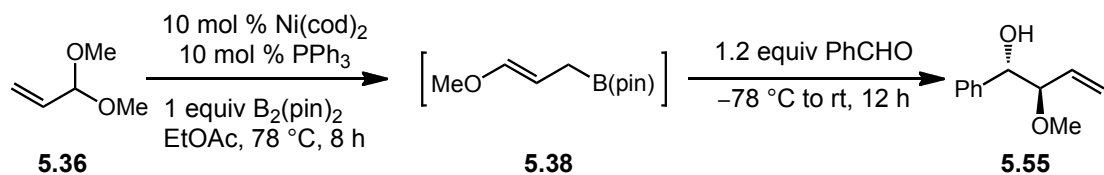
**Proof of Stereochemistry.** The relative configuration was assigned by oxidizing the title compound to the corresponding allylic alcohol **Z-5.63**. The  $^1\text{H}$  and  $^{13}\text{C}$  spectral of **Z-5.63** are in accordance with commercial nerol.



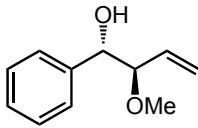
**2-(2-chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.54).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.28 (12H, s,  $(\text{C}(\text{CH}_3)_2)_2$ ), 2.12 (2H, s,  $\text{CH}_2=\text{CClCH}_2\text{B}$ ), 5.11 (1H, s,  $\text{CH}_a\text{H}_b=\text{CCl}$ ), 5.14 (1H, s,  $\text{CH}_a\text{H}_b=\text{CCl}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.7, 83.9, 112.2, 139.2; IR (neat): 2979.6 (w), 2930.8 (w), 1634.1 (w), 1331.1 (w), 1272.9 (w), 1141.4 (s), 968.5 (m), 871.7 (m), 845.6 (m), 671.6 (w), 631.9 (w), 548.6 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_9\text{H}_{17}\text{BClO}_2$   $[\text{M}+\text{H}]$ : calculated: 203.1010, found: 203.1015. The unpurified reaction mixture was purified on silica gel (50:1 pentane/ $\text{Et}_2\text{O}$ ) to afford a clear, colorless oil (69.8 mg, 69% yield).  $R_f$  = 0.52 (8:1 hexanes/ $\text{EtOAc}$ , stain in  $\text{KMnO}_4$ ).

## 8. Representative Procedures for the One-Pot Borylation/Allylboration

### Representative Procedure A:





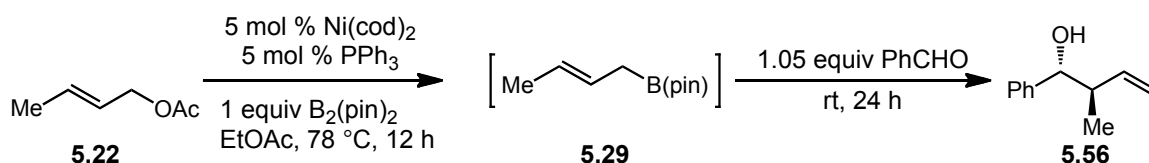


**2-methoxy-1-phenylbut-3-en-1-ol (5.55).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with bis(1,5-cyclooctadiene)nickel(0) (13.8 mg, 0.05mmol), triphenylphosphine (13.1 mg, 0.05 mmol) and EtOAc (1.0 mL) in a dry-box under an argon atmosphere. 3,3-dimethoxyprop-1-ene (51.1 mg, 0.5 mmol) was then added, followed by bis(pinacolato)diboron (127 mg, 0.5 mmol). The vial was capped and sealed, removed from the dry-box, and allowed to stir at 60 °C for 8 hours. The reaction was then concentrated *in vacuo*, cooled to -78 °C and charged with freshly distilled benzylaldehyde (63.6 mg, 0.6 mmol) dropwise. The reaction was capped, allowed to warm to room temperature and stir for another 12 hours. After that period of time, the reaction was diluted with 1:1 mixture of diethyl ether and water, extracted with diethyl ether for three times. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. Analysis of the unpurified reaction mixture through the use of <sup>1</sup>H NMR was used to determine the conversion and the diastereoselectivity of the reaction. The unpurified reaction mixture was purified on silica gel (10:1 hexanes:EtOAc) to afford a clear, colorless oil (78.1 mg, 80% yield). *R<sub>f</sub>* = 0.25 (8:1 hexanes/EtOAc, stain in KMnO<sub>4</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 2.56 (1H, m, OH), 3.33 (3H, s, OCH<sub>3</sub>), 3.78 (1H, m, MeOCHCH=CH<sub>2</sub>), 4.83 (1H, t, *J* = 4.0 Hz, ArCHOH), 5.19 (1H, dq, *J* = 17.5, 1.0 Hz, CH<sub>trans</sub>H<sub>cis</sub>=CH), 5.28 (1H, dq, *J* = 11.0, 1.0 Hz, CH<sub>trans</sub>H<sub>cis</sub>=CH), 5.65 (1H, ddd, *J* = 17.5, 11.0, 8.0 Hz, CH<sub>2</sub>=CH), 7.25-7.28 (1H, m, Ar-H), 7.31-7.35 (4H, m, Ar-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 56.7, 75.3, 86.6, 120.2, 126.7, 127.5, 128.0, 133.6, 140.1; IR

(neat): 3448.7 (w), 2982.0 (w), 2929.4 (w), 2880.7 (w), 2823.7 (w), 1452.1 (m), 1189.1 (m), 1100.8 (m), 1081.6 (m), 1065.1 (m), 989.5 (m), 926.6 (m), 725.1 (m), 697.9 (s)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{11}\text{H}_{18}\text{NO}_2$   $[\text{M}+\text{NH}_4]^+$ : calculated: 196.1337, found: 196.1347.

**Proof of Stereochemistry.** The relative configuration was assigned by comparison of the  $^1\text{H}$  with the literature references.<sup>30</sup>

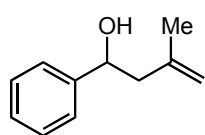
**Representative Procedure B:**



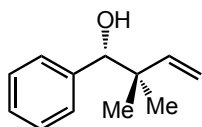
**2-methyl-1-phenylbut-3-en-1-ol (5.56).** An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with bis(1,5-cyclooctadiene)nickel(0) (6.9 mg, 0.025 mmol), triphenylphosphine (13.1 mg, 0.025 mmol) and EtOAc (1.0 mL) in a dry-box under an argon atmosphere. Crotyl acetate (57.1 mg, 0.5 mmol) was then added, followed by bis(pinacolato)diboron (127 mg, 0.5 mmol). The vial was capped and sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. The reaction was allowed to cool to ambient temperature and then charged with freshly distilled benzaldehyde (55.7 mg, 0.53 mmol). The reaction was capped again and allowed to stir for another 24 hours. After that period of time, the reaction was diluted with 1:1 mixture of diethyl ether and water, extracted with diethyl

<sup>30</sup> The *syn*-diastereomer of this molecule has been reported: Brown, H. C.; Jadhav, P. K.; Bhat, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

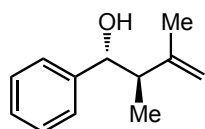
ether for three times. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo. Analysis of the unpurified reaction mixture through the use of  $^1\text{H}$  NMR was used to determine the conversion and the diastereoselectivity of the reaction. The unpurified reaction mixture was purified on silica gel (12:1 hexanes:EtOAc) to afford a clear, colorless oil (64.9 mg, 80% yield).  $R_f = 0.24$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ). Spectral data are in accordance with the literature references.<sup>31</sup>



**3-methyl-1-phenylbut-3-en-1-ol (5.57).** The unpurified reaction mixture was purified on silica gel (12:1 hexanes:EtOAc) to afford a clear, colorless oil (71.3 mg, 88% yield).  $R_f = 0.25$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ). Spectral data are in accordance with the literature references.<sup>32</sup>



**2,2-dimethyl-1-phenylbut-3-en-1-ol (5.58).** The unpurified reaction mixture was purified on silica gel (40:1 hexanes:EtOAc) to afford a clear, colorless oil (44.1 mg, 50% yield).  $R_f = 0.38$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ). Spectral data are in accordance with the literature references.<sup>33</sup>



**2,3-dimethyl-1-phenylbut-3-en-1-ol (5.59).** The unpurified reaction mixture was purified on silica gel (40:1 hexanes:EtOAc) to afford a clear, colorless oil (70 mg, 50% yield) as a mixture of *anti* and *syn* diastereomers (15:1

<sup>31</sup> Katsukiyo, M.; Wang, D.; Hosomi, A.; *J. Am. Chem. Soc.* **2005**, *127*, 9366.

<sup>32</sup> Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916.

<sup>33</sup> Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.

*anti:syn*).  $R_f = 0.27$  (8:1 hexanes/EtOAc, stain in  $\text{KMnO}_4$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.79 (3H, d,  $J = 7.1$  Hz,  $\text{CHCH}_3$ ), 1.79 (3H, m,  $\text{CH}_3\text{C}=\text{CH}_2$ ), 2.27 (1H, d,  $J = 1.7$  Hz, OH), 2.48 (1H, dq,  $J = 9.5, 7.0$  Hz,  $\text{CH}_3\text{CHC}=\text{CH}_2$ ), 4.38 (1H, dd,  $J = 9.5, 1.7$  Hz, ArCHOH), 4.99 (2H, m,  $\text{C}=\text{CH}_2$ ), 7.29-7.37 (5H, m, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.9, 18.5, 50.1, 76.2, 113.7, 127.1, 127.7, 128.3, 142.5, 147.3; IR (neat): 3442.9 (w), 3066.1 (w), 3029.8 (w), 2967.2 (w), 2935.8 (w), 2899.9 (w), 1644.3 (w), 1493.6 (w), 1453.0 (w), 1373.5 (w), 1318.3 (w), 1271.0 (w), 1193.2 (w), 1086.6 (w), 1072.8 (w), 1053.0 (w), 1017.3 (m), 889.4 (s), 834.7 (w), 751.2 (m), 698.3 (s), 628.8 (w), 568.8 (m), 541.3 (w)  $\text{cm}^{-1}$ ; HRMS (ESI+) for  $\text{C}_{12}\text{H}_{15}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]$ : calculated: 159.1174, found: 159.1172.

***Proof of Stereochemistry.*** The relative configuration was assigned by comparison of the  $^1\text{H}$  with the literature references.<sup>33</sup>